British Journal of Anaesthesia

JOINT EDITORS:
E. FALKNER HILL T. CECIL GRAY
Editor of Postgraduate Educational Numbers R. P. HARBORD

Volume XXXII No. 8 August 1960

JOHN SHERRATT & SON : *Publishers*
ALTRINCHAM ENGLAND

Cyprane

specialise in

PRECISION ANAESTHETIC APPARATUS

The present standard products are as follows:—

- **CALIBRATED VAPORIZERS** for volatile anaesthetic agents.
  - FLUOTEC ... ... for "Fluothane" (standard range 0·5%—4·0%).
  - TRITEC ... ... for "Trilene" (standard range 0·5%—1·5%)
  - CHLOROTEC ... ... for Chloroform (standard range 0·5%—5·0%).
  - AZEOTEC ... ... for the azeotropic mixture of "Fluothane" with ether.
- **TECOTA MARK 6 INHALER** for analgesia set to give 0·5% Trilene in air and approved for use by Midwives.
- **THE CYPRANE INHALER** ... for "Trilene" analgesia in midwifery and minor surgery.
- **A.E. GAS-OXYGEN Apparatus** for the administration of nitrous oxide/oxygen (range 0—100%) in Dental and General anaesthesia.

Cyprane Limited

HAWORTH, KEIGHLEY, YORKSHIRE

(*Telephone:* Haworth 3286)

"Trilene" and "Fluothane" are the registered trade marks of Imperial Chemical Industries Ltd., and "Vinesthene" is that of May & Baker Ltd.

PARKINSON COWAN

Laboratory Gas Test Meter

Backed by 150 years of experience in gas test meter design and manufacture

	MAXIMUM CAPACITY								
	WET METERS				DRY METERS				
	A	B	E/40	P13	D1	D4	CD1	CD4	218
cu. ft./rev.	1/50	1/50	1/10	—	2	2	—	—	—
cu. ft./hr.	20	10	40	—	200	400	—	—	190
l./rev.	½	½	2½	½	50	50	10	10	—
l./hr.	500	250	1000	250	5000	10000	6000	11000	5400

Maximum pressure is 10 in. W.G. (254 mm. W.G.) except for Type 218 for which it is 5 p.s.i. (0·35 kg. cm.^{2})

TYPE 'CDI' PORTABLE SPIROMETER

Calibrated in litres. Capacity 6,000 litres per hour. The 'CDI' portable spirometer is used by doctors for assessing the respiratory function and vital capacity of the lungs. It was designed in conjunction with the Medical Research Council to meet the requirements of physiologists and anæsthetists. It is easily portable and simple to use. Modified designs of the 'CDI' are incorporated in various medical breathing apparatus. A removable rubber non-return flap valve prevents air from being sucked back through the meter. It is internally protected against corrosion.

Ask for leaflet T/47 for details of the full range of Test Meters.

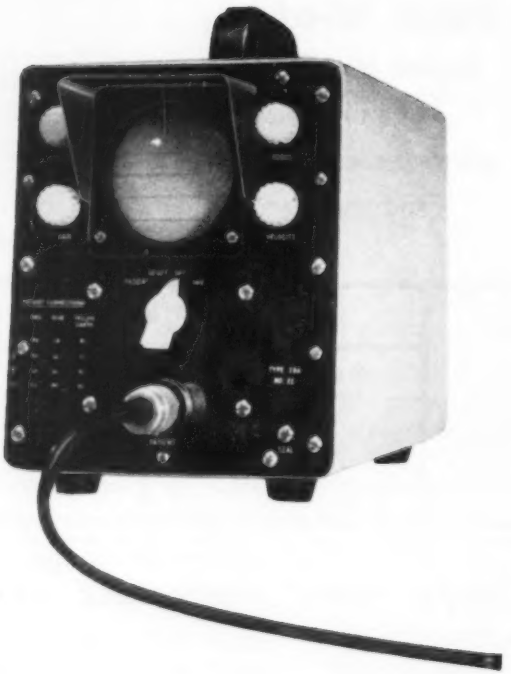
PC PARKINSON COWAN INDUSTRIAL PRODUCTS

(A Division of Parkinson Cowan Ltd.)

Dolphin Works, Fitzalan Street
Kennington Road, London, S.E.11
Telephone : RELiance 2406

Presenting the

VIDEOGRAPH



Designed for routine monitoring of cardiac traces

Can be safely used in the presence of explosive anaesthetic gases

MEDICAL & INDUSTRIAL EQUIPMENT LTD.

SPECIALISTS IN ANAESTHETIC APPARATUS AND SURGICAL INSTRUMENTS

10 & 12 NEW CAVENDISH STREET, LONDON W.1

Telephone : WELbeck 1851 and 1504 *Telegrams : NARCOSIS, LONDON*

MANCHESTER: 152-154 Oxford Road
Phone : ARDwick 5906

•

TORONTO, CANADA: 83-85 Grenville Street
Phone : WALNUT 3-3845

'HIBITANE'

for disinfecting anaesthetic equipment

"Chlorhexidine is regarded as the most suitable disinfectant for anaesthetic equipment."

***Brit. J. Anaesth.* 1959, 31, 363.**

1. Immersion for half an hour in 1 in 1,000 aqueous solution achieves a bacteriologically safe disinfection of equipment such as airways, face masks, endotracheal tubes, etc.

2. A 1 in 5,000 aqueous or alcoholic solution may be used for the sterile storage of instruments, catheters, etc. in the theatre.

3. Emergency disinfection of instruments is achieved by immersing them in 0.5% 'Hibitane' in 70% spirit for one or two minutes.

Hibitane

(chlorhexidine) TRADE MARK

ICI IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION WILMSLOW CHESHIRE

Ph.997

'MEDELEC'

PERIPHERAL NERVE STIMULATOR

An invaluable aid to the anaesthetist

With the increasing use of muscle relaxant drugs, in conjunction with anaesthesia, it has become necessary to stimulate peripheral nerves in order to determine whether in fact the patient is curarized in addition to anaesthetized.

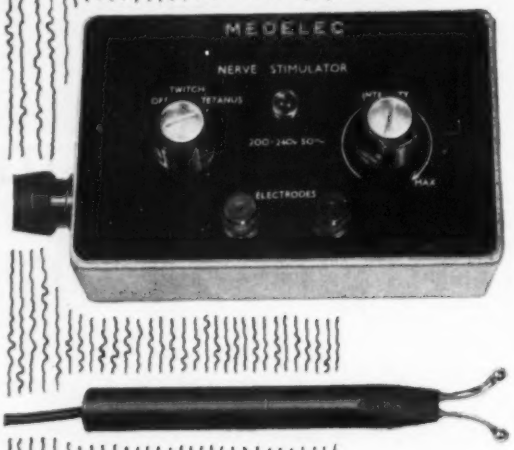
Most anaesthetists are required to determine whether the failure of return of full muscle power is due to a central cause affecting the brain, or to peripheral weakness caused by prolongation of the neuromuscular block.

Electrical stimulation of a peripheral nerve can be made to show whether or not the skeletal musculature responds to impulses.

The MEDELEC apparatus is capable of stimulating at either slow rates (twitch – 3 per second) or fast rates (tetanus – 25 per second).

The unit is extremely compact and simple to use, having only two controls:— an Off/3/25 Impulses/Second switch and an output intensity control. It is gas-tight to prevent the ingress of inflammable anaesthetic agents.

Catalogue No. MED. 120.1



'MEDELEC'

CARDIAC PACEMAKER

This miniature unit has been designed to provide direct cardiac stimulation in the event of a heart block during surgery.

By means of a wire electrode implanted in the heart muscle, controlled electric shocks are applied until the intrinsic heart rhythm is restored. A second electrode (the indifferent), is strapped to, or implanted in, a convenient part of the patient. The output is variable in amplitude from 0 to 12 volts and is delivered at repetition rates of 40 to 120 pulses per minute. Shock pulse duration is approximately 2 milli-seconds.

A special feature of the apparatus is that it will continue to operate in the event of a mains failure. The unit is normally operated from an A.C. supply, but in the event of a power failure, or to facilitate movement of the patient, the unit will continue to operate for a minimum period of three hours.

A miniature moving coil meter is provided to indicate the pulse repetition rate, at the same time enabling a check to be made of the continuity of the electrode system.

Catalogue No. MED. 120.3

Please send for full details to:—

STANLEY COX LIMITED

MEDICAL DIVISION

ELECTRIN HOUSE · 93-97 NEW CAVENDISH STREET · LONDON W.1

Telephone: LANgham 4551-6

Telegrams: STANLICOX Wesdo

'Fluothane' in Prostatectomy

The I.C.I. Film "Prostatectomy under Fluothane" shows the operation in progress. The film is 16 mm. colour, 11 minutes running time, cat. No. M42 and may be borrowed for showing to suitable audiences.

'FLUOTHANE' anaesthesia provides excellent conditions for patients undergoing prostatectomy, and has the important advantage that there is a significant saving of blood loss both during and after the operation.

Other notable features of 'Fluothane' are to be found in a smooth, rapid induction, quiet and easy respiration without laryngeal or bronchial irritation, protection from surgical shock and an uneventful recovery.

With these valuable attributes, 'Fluothane' is considered by many authorities to be especially useful for anaesthesia in elderly, bronchitic and poor-risk cases.

Fluothane - *an I.C.I. discovery*

(Halothane B.P.C.) TRADE MARK

"*Chlorhexidine is regarded as the most suitable disinfectant for anaesthetic equipment.*"
Brit. J. Anaesthesia (1959), 31,363

Chlorhexidine is an I.C.I. antiseptic available under the trade mark HIBITANE.

IMPERIAL CHEMICAL INDUSTRIES LIMITED PHARMACEUTICALS DIVISION WILMSLOW CHESHIRE

ICI

Ph.2

THE INTERNATIONAL MEDICAL ABSTRACTING SERVICE

EXCERPTA MEDICA

AMSTERDAM — NEW YORK

offers to medical science:

For each medical specialty a MONTHLY ABSTRACTING JOURNAL containing abstracts in English from every available medical journal in the world.

Two special publications:

(1) SIDE EFFECTS OF DRUGS: an exhaustive and up-to-date review of the use of present-day drugs and their side effects, edited and compiled by L. Meyler, M.D.

(2) PHARMACOLOGICAL AND CHEMICAL SYNONYMS: a collection of more than 8,000 references from the medical literature of the world, compiled by E. E. J. Marler, M.D., M.Sc., Ph.D.

A TRANSLATION SERVICE for the rapid translation of medical publications and manuscripts.

Address your requests to our sole distributors for Great Britain and the Commonwealth (excluding Canada and South Africa)

E. & S. LIVINGSTONE, LTD. *Teviot Place, Edinburgh, 1*

CANADIAN ANÆSTHETISTS' SOCIETY JOURNAL

Editor

R. A. GORDON, C.D., B.SC., M.D., F.R.C.P.(C), F.F.A.R.C.S.

Editorial Board

ALAN B. NOBLE, M.D., F.A.C.A. — E. A. GAIN, B.A., M.D.

LOUIS LAMOUREUX, M.D. — LEON LONGTIN, M.D., F.R.C.P.(C)

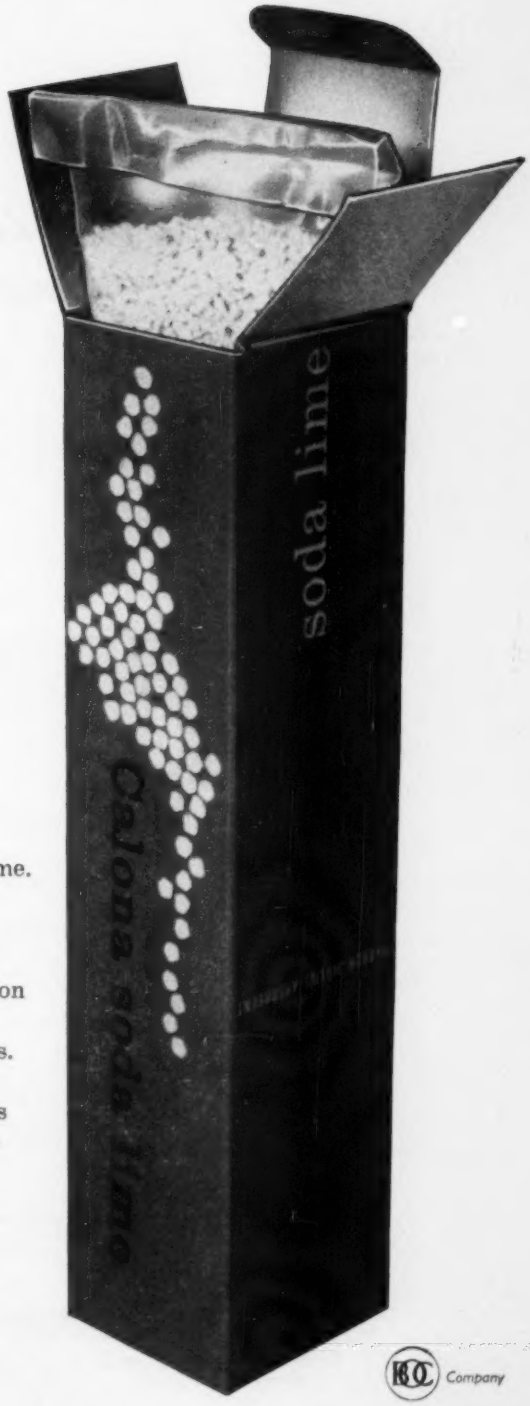
★

The Journal is issued quarterly for members of the Society and Subscribers. It contains original articles and reviews on clinical and basic science subjects related to Anæsthesia.

Annual Subscription $8.00 post paid

The Secretary
Canadian Anæsthetists Society
178 St. George Street, Toronto 5, Ontario, Canada

Calona soda lime gets a new dress



There's an air of practicality about this new 500 gramme pack for Calona soda lime. The strong cardboard carton withstands hard usage—protects Calona from crushing or dusting, and the heavy duty transparent inner pack keeps Calona in first class condition during prolonged storage and enables it to be easily transferred to soda lime canisters. Calona is prepared exclusively for British Oxygen to the stringent requirements of the Company's Research and Development Centre. It is supplied in both standard and colour indicating grades.

BRITISH OXYGEN GASES LIMITED

Medical Division · Great West Road
Brentford · Middlesex

BOC Company

An increased choice

'PHENERGAN'
trade mark brand
PROMETHAZINE HYDROCHLORIDE

combines sedative, anti-emetic and antihistamine actions with a drying effect on secretions.

'SONERGAN'
trade mark brand
PROMETHAZINE/BUTOBARBITONE

a sedative and hypnotic particularly useful on the nights before and after operation.

'VALLERGAN'
trade mark brand
FORTE
TRIMEPRAZINE TARTRATE

for oral pre-anaesthetic medication of children. Only a small quantity of the syrup is required.

M&B *brand Medical Products*

DISTRIBUTORS: PHARMACEUTICAL SPECIA

of premedicants

AND

'PAMERGAN'
trade mark brand
PRE-ANAESTHETIC SOLUTIONS

There are now five carefully selected combinations of promethazine and pethidine with or without scopolamine or atropine in specially prepared ampoules. These presentations eliminate the tedious procedure of mixing the contents of two or more separate ampoules, and the trauma resulting from large or multiple injections.

'PAMERGAN' SOLUTIONS ARE PRESENTED AS—

P.100	PETHIDINE HYDROCHLORIDE B.P. ..... 100 mg. PROMETHAZINE HYDROCHLORIDE B.P. ..... 50 mg. in each 2 ml. ampoule
P.100/25	PETHIDINE HYDROCHLORIDE B.P. ..... 100 mg. PROMETHAZINE HYDROCHLORIDE B.P. ..... 25 mg. in each 1 ml. ampoule
SP.50	SCOPOLAMINE HYDROBROMIDE B.P. ..... 0·43 mg. PETHIDINE HYDROCHLORIDE B.P. ..... 50 mg. PROMETHAZINE HYDROCHLORIDE B.P. ..... 50 mg. in each 2 ml. ampoule
SP.100	SCOPOLAMINE HYDROBROMIDE B.P. ..... 0·43 mg. PETHIDINE HYDROCHLORIDE B.P. ..... 100 mg. PROMETHAZINE HYDROCHLORIDE B.P. ..... 50 mg. in each 2 ml. ampoule
AP.100/25	ATROPINE SULPHATE B.P. ..... 0·6 mg. PETHIDINE HYDROCHLORIDE B.P. ..... 100 mg. PROMETHAZINE HYDROCHLORIDE B.P. ..... 25 mg. in each 1 ml. ampoule

Detailed information is available on request.

MANUFACTURED BY **MAY & BAKER LTD**

MA7542/120

I T I E S (M A Y & B A K E R) L T D · D A G E N H A M

for deep but *controlled* relaxation

SCOLINE

- gives profound muscular relaxation for 2 to 6 minutes
- allows rapid return of spontaneous respiration and normal muscle tone, after use
- does not release histamine nor produce bronchospasm
- is free from toxic effects
- may be used with safety with all known anæsthetic agents
- reduces the risk of bone-fracture during E.C.T.

Scoline contains 50 mg. succinylcholine chloride in each c.c. Supplied in ampoules of 2 c.c. in boxes of 5 and 100 ampoules and in rubber-capped vials of 10 c.c.

STANDARD REFERENCE CARD ON APPLICATION

Manufactured in England by ALLEN & HANBURYS LIMITED LONDON E2

N58/515/H

NOTICE TO CONTRIBUTORS

This Journal is for the publication of original work in all branches of anaesthesia, including the application of basic sciences. The March and September issues deal mainly with material of educational value.

Papers. Papers are accepted on the understanding that they have not been and will not be published in whole or in part in any other journal. They are subject to editorial revision. Manuscripts should indicate the title of the paper, the name, qualifications and full address of the author, and be in double-spaced typing on one side only of quarto paper with a wide margin.

Abbreviations, Weights and Measures. Abbreviations should follow the convention adopted by the *Journal of Physiology*. Weights and measures, dosages, etc., should be expressed in the metric system.

Tables. All tables should be on separate sheets and be capable of interpretation without reference to the text.

Illustrations. Photographs should be unmounted, glossy prints. Drawings, charts and graphs should be in black indian ink on white paper. All illustrations should be clearly numbered with reference to the text on the back and should be accompanied by a suitable legend. The name of the author and title of the paper should also be written on the back of the illustrations.

References. There should be a table of references at the conclusion of the paper. These references should be arranged according to the Harvard system and in alphabetical order. Abbreviations in the references should be according to the World List of Scientific Publications.

In the Harvard system, in the text the year of publication must follow the author's name, more than one paper in any one year being indicated by a small letter (a, b, c) after the date. In the references, the order should be: author's name, followed by initials; year of publication in parentheses; title of paper to which reference is made; title of publication underlined with a single line (to indicate italics) and abbreviated in accordance with the World List of Scientific Periodicals; volume number in arabic numerals, underlined with a wavy line (to indicate bold face); the number of the first page in arabic numerals; thus: Howell, T. H., Harth, J. A. P., and Dietrich, M. (1954). The Use of Chlorpromazine in Geriatrics. *Practitioner*, **173**, 172.

In the case of books, the reference should be as follows: name of author and initials; year of publication in parentheses; title of the book; number of edition; page number; town of origin, publisher; e.g., Hewer, C. L. (1948). *Recent Advances in Anaesthesia and Analgesia*, 6th ed., p. 120, London: Churchill.

The *British Journal of Anaesthesia* should be referred to in the references as *Brit. J. Anaesth.*

Proofs. Proofs will be sent to all contributors. These should be corrected and returned to the Joint Editors within forty-eight hours.

Reprints. Twenty-five reprints of articles will be dispatched to the authors after publication. Further reprints can be supplied if application is made when the proofs are returned.

Copyright. Papers which have been published become the property of the Journal and permission to republish must be obtained from the Editors.

The new potent ANALEPTIC

Vandid

(VANILLIC ACID DIETHYLAMIDE)

. . . increases the frequency and depth of respiration in seconds

MORE POTENT THAN OTHER ANALEPTICS

In animal studies, 'Vandid' was found to be four times more effective than leptazol and fifteen times more effective than nikethamide as a respiratory stimulant. (*Wein Z. inn. Med.*, 1952, 1 : 16)

MORE EFFECTIVE IN BARBITURATE OVERDOSAGE

". . . As a respiratory stimulant bemegride has repeatedly failed in the deeply comatose patient with high blood barbiturate levels. In fact as a respiratory stimulant it would appear to be much less effective than the convulsant vanillic acid diethylamide".
(*Brit. med. J.*, 1959, 2: 1332)

VANDID IS SAFE . . . . DOSAGE IS SIMPLE . . . .

Within the recommended dosage range (1-2 ml) toxic reactions are rarely seen.

RIKER

BASIC N.H.S. PRICES
ampoules (5% solution)
6 x 2 ml 13/-
6 x 5 ml 18/-

'Vandid' is a trade mark

RIKER LABORATORIES LIMITED, Loughborough, Leicestershire

66/2-VI

All enquiries concerning

ADVERTISING SPACE IN THIS JOURNAL

should be addressed to the Advertising Agent

MRS. K. BLOMFIELD
57 CHURCH STREET
OLD ISLEWORTH, MIDDLESEX

Telephone ISLeworth 7788

BOARD OF MANAGEMENT AND PROPRIETORS

General Editors

E. FALKNER HILL, *Late Senior Anaesthetist, Manchester Royal Infirmary*

T. CECIL GRAY, *Professor of Anaesthesia, University of Liverpool*

Editor of Postgraduate Educational Numbers

R. P. HARBORD, *Reader in Anaesthetics, University of Leeds*

Consultant Editors

J. W. DUNDEE, *Senior Lecturer in Anaesthetics, Queen's University of Belfast, Northern Ireland.*

H. H. PINKERTON, *Joint Lecturer in Anaesthetics, University of Glasgow, Scotland*

W. W. MUSHIN, *Professor of Anaesthetics, Welsh National School of Medicine, Wales*

R. F. WOOLMER, *Professor of Anaesthetics, Department of Anaesthesia, Royal College of Surgeons of England, London*

Assistant Editors

A. R. HUNTER, *Consultant Anaesthetist, Manchester Royal Infirmary*

J. E. RIDING, *Demonstrator to the Department of Anaesthesia, University of Liverpool*

M. H. ARMSTRONG DAVISON, *Consultant Anaesthetist, The United Newcastle upon Tyne Teaching Hospitals*
R. C. LAWRENCE, *Consultant Anaesthetist, United Leeds Hospitals.*
T. J. C. MACDONALD, *Consultant Anaesthetist, Aberdeen Royal Infirmary*
A. G. MILLER, *Consultant Anaesthetist, Western Infirmary, Glasgow*
R. J. MINNITT, *Senior Honorary Anaesthetist, Royal Liverpool United Hospitals*
R. E. PLEASANCE, *Lecturer in Anaesthetics, University of Sheffield*
H. Q. O. WHEELER, *Consultant Anaesthetist, Department of Neurological Surgery, General Hospital, Sunderland.*
W. D. WYLIE, *Consultant Anaesthetist, St. Thomas's Hospital, London*

Papers for publication and all editorial communications should be addressed to either of the Editors at 48–50 Bedford Street North, Liverpool, 7. Business communications should be addressed to the publishers: JOHN SHERRATT AND SON, Park Road, Altrincham, Cheshire.

Published monthly. Annual subscription (post free): Inland £3 15*s.*; Overseas £4 4*s.*; United States and South Americas $12.00.

© John Sherratt and Son, 1959.

Further progress in Hospital Instruments

BURNDEPT BE.277

BODY PULSE METER

Battery operated (truly portable)—sensitive—reliable and simple to use. Inexpensive.

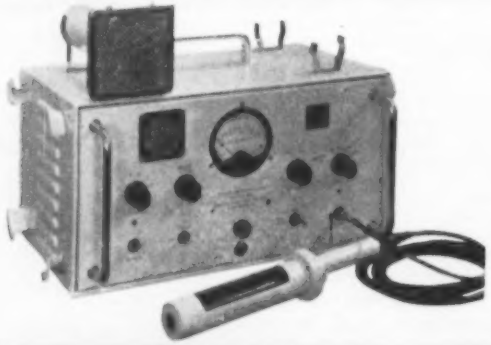
Brief specification:
Visual Indication of Arterial Pulsation. A Microphone acting as a transducer, applied to the pulp of the terminal phalanx of any digit is used to operate the meter which thus indicates the arterial pulsations.
In conjunction with a sphygmomanometer it can be used to measure systolic blood pressure, the BE. 277 taking the place of the stethoscope.

BURNDEPT BN.120

Universal Scintillation Counter

A truly adaptable instrument which allows for several types of Collimators, different grades and types of Crystals, thus making it a multi-purpose Scintillation Counter.
A Cathode Follower and Head Amplifier are available, designed to be truly compatible, comprising:

Lead Skirt BN 125 Wide Angle Collimator BN 122
Narrow Angle Collimator Attachment BN 124
Slotted Collimator BN 126 Adjustable Clamp BN 121
Adjustable Clamp BN 123 Cathode Follower Unit BN 127
Connectors



BURNDEPT BN.110 (AERE Cat. No. 3-7/15544)

General Purpose Ratemeter Mk. II

Associated Probes: Alpha—BN. 111.
Beta/Gamma—BN. 108.

Brief Specification: Designed primarily for measuring the radiation from contaminated surfaces.
Two probes are used for the detection of radiation.
A Large Area Alpha Probe BN. 111 operating on the scintillation counter principle.
A Beta/Gamma Probe BN. 108 using a thin walled Geiger tube.
Ranges of 0-5, 0-50, 0-500 and 0-5000 counts/sec.

BURNDEPT BN.106

Head Amplifier—(for use with BN. 110 & BN. 120).

Brief specification: A wide band linear amplifier for amplifying pulses having a short development time.
Small and compact and very suitable for use between scintillation counter or ion chambers and ratemeters or scalers.

Enquiries to: CONTRACT SALES DEPT., BURNDEPT LIMITED, ERITH, KENT. Telephone: Erith 33080

"I would have everie man write what he knowes and no more."—MONTAIGNE

BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXII No. 8 AUGUST 1960

EDITORIAL

THE ANAESTHETIST AND CHRONIC PAIN

AN encouraging feature of the contemporary anaesthetic scene is the evidence of a gradually increasing interest in the management of patients with chronic pain. Although the pain of malignant disease immediately springs to mind, even brief acquaintance with a Pain Clinic suffices to emphasize the appreciable problem presented by patients suffering, for example, from post-herpetic neuralgia or postoperative neuralgia.

The anaesthetist, by virtue of his knowledge of local analgesic procedures, is well placed to offer his aid to these unfortunates. Unhappily, he may all too often find that while permanent relief is elusive following repeated blocks with short acting substances, a neurolytic agent is contra-indicated because of the possibility of permanent disability and of recovery neuritis. A drug capable of temporarily interrupting conduction for a matter of weeks is not yet available.

The usefulness of alcohol in the management of chronic pain has been recognized for many years and yet in many centres it is practised on a very small scale in comparison with the size of the problem. Bonica (1953) in particular has done great service by his publication of meticulous and painstaking subarachnoid techniques. Recently, Maher (1955, 1957, 1960) has advocated the use of phenol in glycerine or Myodil in the management of cancer, and his lead has been followed by others. Although perhaps not all can emulate the remarkable success described by Maher, there can be no doubt in the minds of those with experience of his technique that it is simple, remarkably free from serious side effects, and deserves more extensive use.

Apart from injection techniques the anaesthetist's help is increasingly sought in the administration of analgesic drugs. As Dundee (1957) observed, "... in no other branch of medicine does the training require so intimate a knowledge of the actions of powerful narcotics and analgesics. . . ." Although the success of a well chosen and executed block is more to be desired than relief dependent upon analgesics with their associated side effects, this is by no means always possible. The use of additional drugs with the object of extending or modifying analgesic action is now well established. New analgesics are constantly appearing, and in their evaluation anaesthetists have made many noteworthy contributions. The value of a pain clinic in the controlled assessment of pain-relief measures is self-evident.

It may be hoped that more anaesthetists will interest themselves in this important field, not only in regard to the use of nerve blocks, but in the management of patients as a whole. It is perhaps insufficiently appreciated by anaesthetists that their specialized knowledge and skill can help a proportion of their patients who have failed to obtain relief after prolonged investigation and treatment by their colleagues in other fields. With patience and care considerable satisfaction can be gained by endeavours in this field, but frequent disappointments are to be expected. However, these must not be allowed to discourage. Incomplete or temporary success is common, but the chronic sufferer is often helped.

It seems reasonable to hope that gradually all medical centres of any size will include a Pain Clinic, whether controlled by a medical committee including anaesthetists or by anaesthetists to whom suitable patients are referred by their consultant colleagues.

REFERENCES

Bonica, J. J. (1953). *The Management of Pain*. Philadelphia: Lea and Febiger.

Dundee, J. W. (1957). Adjuvants in the relief of chronic pain. *Anaesthesia*, **12**, 330.

Maher, R. M. (1955). Relief of pain in incurable cancer. *Lancet*, **1**, 18.

—— (1957). Neurone selection in the relief of pain. *Lancet*, **1**, 16.

—— (1960). Further experiences with intrathecal and subdural phenol. *Lancet*, **1**, 895.

Brit. J. Anaesth. (1960), 32, 346

THE SOLUBILITY OF VOLATILE ANAESTHETICS IN OIL

BY

J. F. NUNN

Research Department of Anaesthetics, Royal College of Surgeons of England, and Department of Anaesthetics, Postgraduate Medical School, University of London

THE oil solubility of an anaesthetic is of interest for at least two reasons. Firstly, it governs the passage of the agent into and out of the fat depots of the body. Secondly, there is a correlation between the potency of an agent and its solubility in oil. In figure 1 an inverse relationship is shown between the concentration required for narcosis and the solubility in oleyl alcohol determined by Meyer and Hemmi (1935). A similar relationship was found, covering seventeen volatile narcotics, by Meyer and Hopff (1923). This correlation is considerably closer than with the more familiar oil-water solubility ratio which forms the basis of the well-known Meyer-Overton generalization (fig. 2).

However, the concept of the fat solubility of an anaesthetic is not without difficulty since it may easily be verified that the common volatile liquid agents are miscible with oil in all proportions. It would thus *appear* difficult to ascribe to them a finite solubility or, indeed, to compare the solubility of one with another. We have therefore carried out further studies of the solubility of a typical anaesthetic in oil, bearing in mind that in the liquid state the solubility is infinite. This paper describes this work and discusses certain applications of the findings.

METHODS

In these experiments chloroform was chosen as a typical volatile anaesthetic and there would appear to be no reason for believing that it behaves differently from other agents. After the example of Meyer and Hemmi (1935), oleyl alcohol (octadecanol) was selected as a typical oil—having the additional advantage of being a pure chemical substance.

The first experiment was suggested by Dr. C. Long and consisted of the exposure of oil to chloroform vapour at a partial pressure equal to its saturated vapour pressure at the temperature of the oil. This was achieved simply by placing a beaker of chloroform (70 ml) inside a sealed jar containing 5 ml of oil. The uptake of chloroform by the oil was measured by noting the increase in volume of the oil. In the hope of accelerating the uptake, the surface area of the oil was increased with a small wick of filter paper.

The second series of experiments consisted of the exposure of oil to chloroform vapour at a partial pressure less than its saturated vapour pressure at the temperature of the oil. The chloroform vapour was prepared by saturating a carrier gas (oxygen) with chloroform vapour at a known temperature below that of the oil. The partial pressure of chloroform could then be determined from vapour pressure tables. The gas stream was bubbled through oil over a sintered disc until equilibrium was attained (fig. 3).

It was shown, by determination of dew point, that with flows of carrier gas up to 250 ml/min, the issuing vapour was better than 99 per cent saturated at the temperature of the water bath. Since it was not convenient to maintain the bath at temperatures below 0°C., tensions of chloroform less than 60 mm Hg (fig. 4) were attained by dilution of the carrier stream.

The concentration of chloroform in the oil was determined at intervals during the procedure by weighing 5 ml samples of the oil/chloroform mixture. One per cent chloroform corresponded to an increment of the order of 30 mg which could be determined without difficulty. It was shown that, within the limits of accuracy of the study, the specific gravity of the mixture bore a linear relation to the concentration of chloroform in the mixture.

RESULTS

When oil was exposed to chloroform at its saturated vapour pressure equilibrium was not

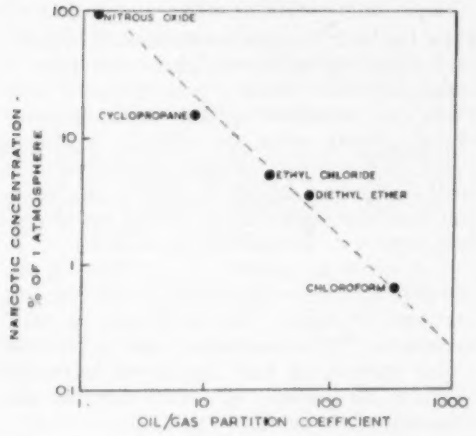


FIG. 1

Narcotic concentrations of various anaesthetic agents plotted against fat solubility. With the logarithmic co-ordinates an inverse relationship is indicated by a straight line of slope minus one. Fat solubility is expressed as the oil/gas partition coefficient determined for oleyl alcohol by Meyer and Hemmi (1935). The value for cyclopropane is taken from Adriani (1946). Isonarcotic concentrations for mice are taken from Meyer and Hopff (1923) and for man from various standard textbooks of anaesthesia.

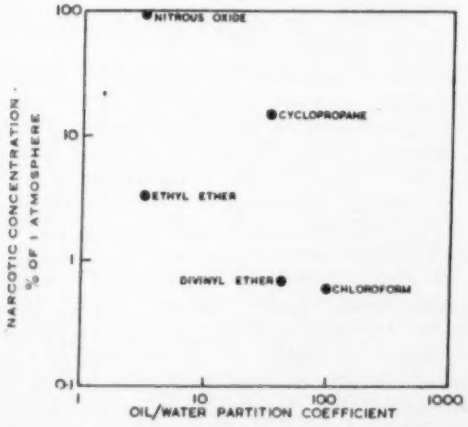


FIG. 2

Narcotic concentrations of various anaesthetic agents plotted against oil/water solubility ratios. With the logarithmic co-ordinates an inverse relationship would be indicated by a straight line of slope minus one. Oil/water solubility ratios are taken from Lee (1953) and narcotic concentrations as for figure 1.

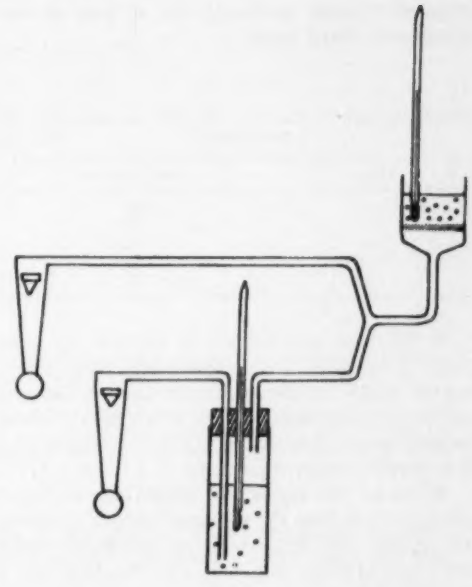


FIG. 3

A modified "copper kettle" for preparing dilute chloroform vapour and passing it through oil in a sintered funnel. To ensure saturation, the vaporizer consisted of two chambers, one of which is not shown in the diagram.

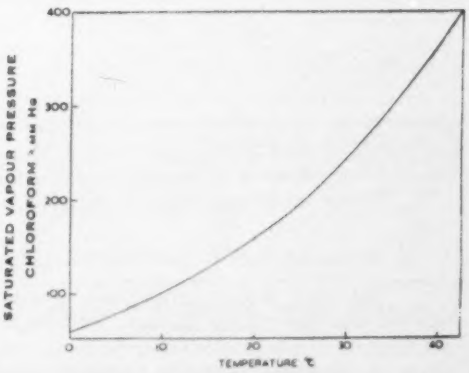


FIG. 4

Saturated vapour pressure curve of chloroform.

obtained. Uptake continued for as long as the experiment lasted (table I).

TABLE I

Uptake of chloroform by 5 ml oleyl alcohol at room temperature.

Days	Chloroform
	ml
7	25
16	34
35	48
54	56

In 54 days, unit volume of oil took up more than 10 volumes of chloroform and there would appear to be no reason for considering that the uptake is other than infinite although the actual rate of uptake is exceedingly slow compared with the uptake of gases by water.

When oil was exposed to chloroform at partial pressures less than the saturated vapour pressure, the uptake was finite with an end-point which was well-marked although not reached for a number of hours. The existence of the end-points was confirmed by starting with oil-chloroform mixtures above and below the equilibrium mixture. During exposure to a given partial pressure, the weak mixtures became stronger and the strong mixtures weaker until all ended up at the same concentration. From the figures for the uptake of chloroform at various partial pressures, it was possible to calculate the apparent solubility coefficient at each experiment (table II).

TABLE II

Solubility of chloroform in oleyl alcohol at 20°C.

Partial pressure of chloroform in gas phase	% chloroform in oil/chloroform mixture	Apparent Ostwald solubility coefficient
mm Hg		
160	>90	>12,000
122	33	910
65	14	570
35	7	480

Saturated vapour pressure of chloroform at 20°C is 160 mm Hg.

Thus the apparent solubility coefficient rises towards infinity as the partial pressure of chloroform approaches its saturated vapour pressure.

DISCUSSION

There can be little doubt that the uptake of chloroform vapour by oil is not comparable with its uptake by water. There is gross deviation from Henry's law at tensions approaching the saturated vapour pressure, when the solubility coefficient clearly rises towards infinity. Nevertheless, at lower tensions of chloroform vapour, the deviation from Henry's law is less marked and chloroform *appears* to have a finite oil solubility.

It is useful to approach the problem of the solubility of volatile anaesthetics in oil from the standpoint of Raoult's law which may be stated as follows: *In a solution of two liquids, the vapour pressure of each constituent is proportional to the number of mols present in unit volume of the solution.*

From this it follows that the vapour pressure of each component is equal to the saturated vapour pressure of the pure substance multiplied by the mol fraction in which it exists in the solution. That is to say:

$$p = p_0.X$$

where p is the pressure exerted by one component of the mixture;

p_0 is the saturated vapour pressure of the pure substance at the temperature of the mixture;

X is the mol fraction at which it exists in the mixture.

Thus, in an equimolar mixture of ethyl alcohol and water, i.e. one containing 46 grams of alcohol to 18 grams of water, the vapour pressure of each constituent should be half its saturated vapour pressure in the pure state at that temperature.*

In practical application, it is not convenient to consider mol fractions. Volume fractions may be used provided that correction is made for the fact that equal numbers of molecules of different liquids usually occupy different volumes, even under the same conditions of temperature and pressure, i.e. liquids do not conform to Avogadro's hypothesis. Thus the pressure exerted by an anaesthetic in an anaesthetic/oil mixture should equal:

$$p_0 \left(\frac{F.V_{an}}{F.V_{an} + V_{oil}} \right)$$

* Although alcohol/water is a familiar example, it is perhaps unfortunate as it shows a marked deviation from Raoult's law.

where V_{an} is the volume of anaesthetic (liquid) in the mixture;
V_{oil} is the volume of oil in the mixture;
F is the mol volume of oil divided by the mol volume of the anaesthetic.

When the anaesthetic vapour is in equilibrium with an anaesthetic/oil mixture, this expression must equal the partial pressure of the anaesthetic in the gas phase.† Thus:

$$p_{an} = p_o \left(\frac{F.V_{an}}{F.V_{an} + V_{oil}} \right)$$

Where p_{an} is the partial pressure of the anaesthetic in the gas phase.

To determine from this equation the volume of anaesthetic taken up by unit volume of oil, we may clear and solve for V_{an}/V_{oil}:

$$\frac{V_{an}}{V_{oil}} = \frac{p_{an}}{(p_o - p_{an})\,F} \qquad \ldots\ldots\ldots\ldots(i)$$

From this equation it is possible to derive the uptake of an anaesthetic by oil provided three quantities are known: p_o (the saturated vapour pressure of the pure anaesthetic) varies only with the temperature of the experiment; p_{an} (the partial pressure of the anaesthetic in the gas phase) is the variable with which we are concerned; F (the ratio of the mol volumes) may be derived from the molecular weights and specific gravities of the two liquids.

There are three interesting features of the equation. Firstly, no solubility factor as such enters the expression. Secondly, different oils will have different uptakes only in so far as their mol volumes vary. Thirdly, when the partial pressure of anaesthetic in the gas phase equals its saturated vapour pressure at the temperature of the oil, the denominator of the right-hand side is zero and the uptake therefore is infinite. This has already been suspected from the first experimental study.

Equation (i) may be used to plot the uptake of chloroform by oleyl alcohol for various partial pressures of chloroform (fig. 5). Since it is impossible to plot infinity, the ordinate expresses not the ratio V_{an}/V_{oil} but the percentage of chloroform in the mixture. The relationship is represented by a curve rising to show 100 per cent chloroform in equilibrium with chloroform vapour at 160 mm Hg which is the saturated vapour pressure of the pure substance at 20°C. Figure 5 also shows the results of the experimental studies. These too appear to lie along a curve which is shown by the broken line. This has the same general shape as the theoretical curve but is quantitatively somewhat different at the higher tensions. This is to be expected as most pairs of miscible liquids deviate from Raoult's law—possibly giving minimum or maximum boiling point mixtures. Nevertheless, the agreement is generally satisfactory, particularly at the lower ranges, which are of clinical interest. It will also be seen that over the clinical range of pressures, the curve approximates to a straight line and it might appear as though the absorption obeys Henry's law, with a solubility coefficient related to the limiting slope of the curve.

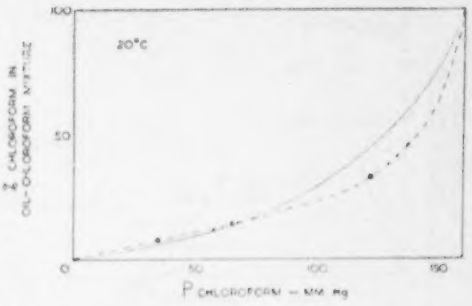


FIG. 5

The continuous line shows the theoretical relationship between partial pressure of chloroform in the gas phase and the percentage of chloroform in a chloroform/oil mixture which is in equilibrium with the gas phase. The curve refers to 20°C. when the saturated vapour pressure of pure chloroform is 160 mm Hg. The solid circles indicate the results derived experimentally.

APPLICATIONS OF THE EQUATION

Uptake of anaesthetics by body depot fat.

Equation (i) may be used to calculate the ultimate uptake of anaesthetic by the body depot fat, assuming that p_{an} of the depot fat comes to equal p_{an} of the arterial blood which will itself ultimately equal p_{an} of the inspired gas mixture.

† Strictly speaking the fugacities will be equal rather than the pressures, although it is unlikely that this is a serious source of error.

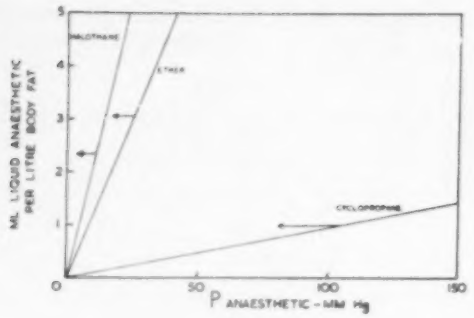


FIG. 6

The equilibrium uptake of three anaesthetics by body fat. The arrows indicate fat uptake at isonarcotic tensions.

Three factors require to be known. Firstly, there is p_0, (saturated vapour pressure of the pure anaesthetic at body temperature). Secondly, F (ratio of the mol volumes of fat and the anaesthetic) may be derived from the molecular weight and specific gravities of the two substances. If it is assumed that body depot fat consists of equal parts of triolein, tri-palmitin and tri-stearin it will be found that F approximates to 10 for most of the commonly used inhalational anaesthetic agents. The final variable is p_{an} (the partial pressure of the anaesthetic in the inhaled gas mixture) and this is, or should be, known to the anaesthetist.

Figure 6 shows the equilibrium uptake of three anaesthetics, per unit volume of body fat, over the clinical range. The curves are all virtually indistinguishable from straight lines and the limiting slopes are functions of the vapour pressures. It is of interest that, at isonarcotic pressures of the anaesthetics, the equilibrum uptakes should be all of the same order as was suggested by Meyer and Hemmi (1935).

It may be shown that, for a man with 10 litres of body fat, equilibration with 1.5 per cent. halothane vapour will result in the uptake of some 25 ml of liquid halothane by the depot fat. It may be presumed that the uptake of halothane is an exponential process and, since the initial charging rate is of the order of 1 ml liquid halothane in 15 minutes, the time constant would appear to be approximately 6 hours. Thus 18 hours would be required for 95 per cent saturation of the body fat and, during an anaesthetic of average duration, the body fat would be barely 25 per cent saturated. These figures are not in conflict with the observations of Duncan and Raventós (1959).

The depth of anaesthesia is probably closely related to the tension of the agent in the arterial blood (Haggard, 1924). Prediction of this quantity is difficult as it would appear to lie between the tension in the inspired gas and the tension in the depot fat. Assuming that the body water compartments soon reach equilibrium with arterial blood, the body may be represented as two resistance-capacitance networks in series (fig. 7). The tension of anaesthetic in the inspired gas mixture is represented by the charging voltage and the first resistance corresponds to alveolar ventilation, diffusing capacity, blood flow and such other factors which influence the uptake of anaesthetic by the body water compartment. The voltage attained across the first capacitance represents the arterial anaesthetic tension. This charge is

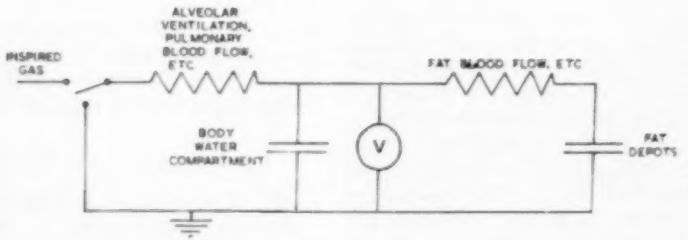


FIG. 7

An electrical analogy of the uptake of anaesthetic agents by the water and fat compartments of the body. The voltmeter (V) is measuring a potential which is analogous to the tension of the anaesthetic in the arterial blood.

steadily leaking away through the high resistance representing fat blood flow, blood/fat barrier, etc., into the very large capacitance which represents the product of the volume of the body fat and the "solubility" in it of the anaesthetic.

It is, of course, by no means clear whether the body water compartment can be represented by a single capacitance separated from the inspired gas by a single resistance. Uptake and elimination by the lungs will be in accordance with the Bohr equation and the Fick principle, neither of which is easy to represent in an electrical analogy. Nevertheless, for agents such as chloroform and halothane, it would appear that the first resistance and capacitance are small in comparison with the second pair (Raventós, 1959) and therefore it may well be reasonable to consider the components of the first pair as though they were a simple RC network. Much experimental work is needed to quantify these systems but the concept of fat solubility discussed in this paper defines the capacitance of the second system and suggests how its time constant may be determined.

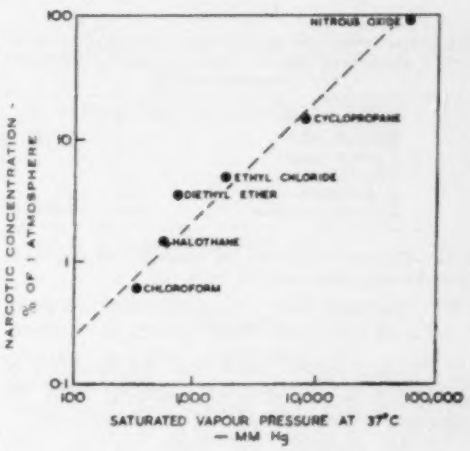


FIG. 8

Narcotic concentrations of various anaesthetic agents plotted against the vapour pressure at 37°C. With the logarithmic co-ordinates a direct relationship is indicated by a straight line of slope plus one. The narcotic concentrations are derived as for figure 1.

Fat solubility and anaesthetic potency.

There is a voluminous literature on the correlation of fat solubility and anaesthetic potency. Meyer and Hemmi (1935) suggested that narcosis occurs if any chemically indifferent substance penetrates into the lipid alcohols of the cell substance in a certain molar concentration which in tadpoles was found to be 0.03 mol/l. From this it follows that there must be a close correlation between narcotic potency and the molar solubility of the agent in oleyl alcohol which was the oil used in their studies.

From equation (i) it will be apparent that the solubility of different anaesthetics in a given oil $\left(\frac{V_{an}}{V_{oil}} \div p_{an}\right)$ will be roughly proportional to the mol volume of the anaesthetic divided by its vapour pressure (provided p_{an} is small compared with p_o). Since the mol volume of anaesthetic agents does not vary widely, the quantity measured by Meyer and Hemmi was roughly related to the reciprocal of the vapour pressure. This work was therefore in accordance with the subsequent demonstration by Ferguson (1939) of the correlation between the narcotic concentration of an agent and its saturated vapour pressure (fig. 8). These papers confirm that the solubility of anaesthetics in oil does in fact obey Raoult's law over the clinical range (Mullins, 1954).

The oil-water solubility coefficient.

From equation (i) it may be shown that the oil-water solubility coefficient of an agent equals:

$$\frac{K}{p_o \lambda}$$

where λ is the Ostwald solubility coefficient for the vapour of the agent in water;

p_o is its saturated vapour pressure in the pure state at the temperature of the experiment;

K is a constant which may be evaluated for any given oil (in the case of oleyl alcohol it is 56,000).

Values for the oil-water solubility coefficient may then be calculated for some of the common anaesthetic agents and it will be found that the calculated results are in reasonable relation to the quoted values which have been determined experimentally (table III).

TABLE III

Calculated values for the oil-water solubility ratios of certain anaesthetic agents. The oil is oleyl alcohol and the temperature 20°C.

Nitrous oxide	2.2
Diethyl ether	3.3
Cyclopropane	39
Chloroform	50
Halothane*	220
Trichloroethylene	400

* The Ostwald coefficient for solubility of halothane in water has been assumed to be 1.0.

SUMMARY

(1) Practical studies show that the solubility of chloroform in oil deviates markedly from the behaviour expected according to Henry's law.

(2) An equation has been derived from Raoult's law from which it is possible to predict the solubility of chloroform in a given oil. Over the clinical range the predicted results agree well with those derived experimentally.

(3) The equation enables the equilibrium uptake of anaesthetic by the body fat to be determined theoretically and quantifies the action of the depot fat as a capacitance.

(4) At a first approximation, the apparent solubility of an anaesthetic in fat is related to the reciprocal of its vapour pressure. Thus the observations of Meyer and Hemmi (1935) are in accord with the expression of potency in terms of chemical potential (Ferguson, 1939).

(5) The equation may be used to derive the oil-water solubility coefficient of anaesthetic agents and the predicted values are in accord with those determined experimentally.

APPENDIX

Raoult's Law. In a solution of two liquids, the vapour pressure of each constituent is proportional to the number of mols present in unit volume of the solution.

Mol fraction of any constituent in a mixture is defined as the number of mols, or gram molecules, of that constituent divided by the total number of mols, or gram molecules, in the mixture.

Henry's Law. The amount of a given gas which dissolves in a given liquid is directly proportional to the pressure of the gas.

Ostwald solubility coefficient (λ). The volume of gas which dissolves in unit volume of solvent measured under the conditions of temperature and partial pressure at which solution takes place.

Derivation of expression for oil/water solubility ratio.

It is assumed that when partition is complete the tension of anaesthetic in the oil phase equals the tension of anaesthetic in the water phase. It is also assumed that the volume of (liquid) anaesthetic is small in comparison with the volume of oil. When this is not true, the expression is very much more complicated and the ratio is not a constant but varies with the tension of the anaesthetic.

Tension of anaesthetic in oil phase.

$$= p_o \times \frac{\text{gram mols anaesthetic}}{\text{gram mols oil}} \qquad \text{(Raoult's Law)}$$

$$= p_o \times \frac{1}{22.400} \times \frac{\text{M. W. (oil)}}{\text{S. G. (oil)}} \times \frac{\text{vols anaes. (vapour)}}{\text{vols oil (liquid)}} \qquad \text{.....(ii)}$$

Tension of anaesthetic in water phase

$$= \frac{760}{\lambda} \times \frac{\text{vols anaes. (vapour)}}{\text{vols water (liquid)}} \qquad \text{.....(iii)}$$

Equating (ii) and (iii) and clearing and solving for

$$\frac{\text{vols anaes.}}{\text{vols oil}} \div \frac{\text{vols anaes.}}{\text{vols water}}$$

the oil/water solubility ratio equals

$$760 \times 22.400 \times 1.04 \times \frac{\text{S. G. (oil)}}{\text{M. W. (oil)}} \times \frac{1}{\lambda \cdot p_o}$$

(correcting volumes of anaesthetic in oil to 20°C).

For oleyl alcohol the oil/water solubility ratio will equal

$$\frac{56.000}{\lambda \cdot p_o}$$

It is assumed that the anaesthetic vapour obeys the gas laws although it is unlikely that this is strictly true.

ACKNOWLEDGMENTS

I am grateful for helpful discussions with Professor W. D. M. Paton, F.R.S., Dr. C. Long and Dr. J. Raventós.

REFERENCES

Adriani, J. (1946). *The Chemistry of Anaesthesia*, p. 126. Oxford: Blackwell Scientific Publications.

Duncan, W. A. M., and Raventós, J. (1959). The pharmacokinetics of halothane (Fluothane) anaesthesia. *Brit. J. Anaesth.*, **31**, 302.

Ferguson, J. (1939). The use of chemical potentials as indices of toxicity. *Proc. roy. Soc.*, **127**, 387.

Haggard, H. W. (1924). The absorption, distribution and elimination of ethyl ether III. *J. biol. Chem.*, **59**, 771.

Lee, J. A. (1953). *A Synopsis of Anaesthesia*, 3rd *ed.* Bristol: John Wright & Sons Ltd.

Meyer, K. H., and Hemmi, H. (1935). Beiträge zur Theorie der Narkose III. *Biochem. Zeitschr.*, **277**, 39.

—— Hopff, H. (1923). Theorie der Narkose durch Inhalationsanästhetika. *Zeitschrift f. physiol. Chem.*, **126**, 281.

Mullins, L. J. (1954). Some physical mechanisms in narcosis. *Chem. Rev.*, **54**, 289.

Brit. J. Anaesth. (1960), **32**, 353

CHANGES CAUSED BY ANAESTHESIA IN THE BLOOD ELECTROLYTES OF THE DOG

BY

D. E. STEVENSON

School of Veterinary Medicine, University of Cambridge, England

THERE have been few studies concerning the effects of anaesthesia on the inorganic blood constituents and much of this work has yielded conflicting results. However, a knowledge of such effects is important when assessing changes which are caused by such differing factors as variations in the carbon dioxide tension of the blood or by the use of drugs such as the muscle relaxants.

The effects of anaesthesia on the total plasma calcium concentration were extensively studied by Cloetta and his fellow workers (Cloetta and Thomann, 1924; Brauchli and Schnider, 1929; Cloetta, Fischer and van der Loeff, 1934, 1942) who believed that during narcosis in many species, including man, there was a consistent decrease of up to 10 per cent of the pre-anaesthetic concentration. They also believed that the speed at which this fall occurred depended on the rapidity of action of the anaesthetic agent used. The consistency of the results published by these workers has not, however, been confirmed by other investigators. Eisler, Geness and Dienerstein (1929) and Lipow, Weaver and Reed (1929) reported a variable decrease in the plasma calcium concentration of dogs subjected to ether anaesthesia, while Emerson (1928) and Andrews, Petersen and Klein (1930) observed an increase in concentration. Mollaret, Pocidalo, Lissac and Demongeot (1956) were unable to demonstrate any significant changes in the plasma calcium concentration during diffusion respiration in anaesthetized dogs, but Brown and Prasad (1957) found an increased concentration in dogs inspiring high concentrations of carbon dioxide for prolonged periods. These workers have also studied changes in ultrafiltrable calcium concentrations during carbon dioxide administration. Unfortunately their methods of determination were not sensitive to changes in the ultrafiltrable, but unionized, plasma calcium. This fraction which is normally considered insignificant may greatly increase when there is an accumulation of acid metabolites, such as lactate, in the body.

Reports concerning magnesium are again conflicting. Lipow, Weaver and Reed (1929) and Cloetta, Fischer and van der Loeff (1934) found great variations in the plasma magnesium concentration as a result of various types of anaesthesia. However, Agnoli (1929), Eisler, Geness and Dienerstein (1929), and Marenzi and Gerschman (1933) reported a consistent decrease in magnesium concentration. Changes in the total and ultrafiltrable plasma magnesium concentrations during the administration of carbon dioxide in the respiratory gases of anaesthetized dogs have been studied by Prasad, Flink and Brown (1957).

The early reports of a decreased potassium concentration during anaesthesia in the dog by Lipow, Weaver and Reed (1929) and Eisler, Geness and Dienerstein (1929) have been repeatedly confirmed (Andrews, Petersen and Klein, 1930; Gerschman and Marenzi, 1933a, b; Robbins and Pratt, 1936; Fay, Andersch and Kenyon, 1939a, b; Larson and Brewer, 1939; Brewster, Bunker and Beecher, 1952). The decrease in concentration caused by ether anaesthesia in the dog may be inhibited by 2, 4 dinitrophenol (Larson and Brewer, 1939) or by high epidural nerve block (Brewster, Bunker and Beecher, 1952).

The plasma sodium concentration has been examined in the anaesthetized dog by Lipow, Weaver and Reed (1929), Marenzi and Gersch-

man (1933), and Fay, Andersch and Kenyon (1939a, b), who reported a small but inconsistent decrease in concentration.

The changes in plasma inorganic phosphate during anaesthesia which have been reported are variable. Stehle and Bourne (1924) believed that in dogs ether anaesthesia produced little change, similar findings also being reported about the same time for man (Potter, 1925). On the other hand Bolliger (1926) believed that ether anaesthesia in dogs reduced the concentration of plasma inorganic phosphate, except when partial asphyxia was present. Similar findings were recorded by Eisler, Geness and Dienerstein (1929). Fay, Andersch and Kenyon (1939a), however, found that the mode of administration of ether anaesthesia to dogs was important in this respect, since ether given by open drop caused a decrease, and by closed-circuit methods an increase, in the plasma inorganic phosphate. These workers (1939b) also found an increase during cyclopropane anaesthesia in dogs. An increase in the plasma inorganic phosphate of man during anaesthesia has been reported by Waters and Schmidt (1934) and Foldes, Murphy and Wilson (1950).

Ether anaesthesia always causes a decrease in the blood pH of dogs which is accompanied by a decreased alkali reserve, whether or not a respiratory acidosis is also present (Dripps and Severinghaus, 1955). Cyclopropane has also been shown to cause a decrease in the blood pH of dogs (Fay, Andersch and Kenyon, 1939b).

METHODS

Carotid arterial loops were prepared in healthy young mongrel dogs, weighing 8 to 20 kg.

At the beginning of an experiment, the dog to be used was premedicated with 0.5 mg/kg body weight pethidine hydrochloride and atropine sulphate 0.65 mg. About 1 hour later, one siliconed 19 S.W.G. hypodermic needle was inserted into the carotid artery, a similar needle also being placed in a cephalic vein. The dog was heparinized with a dose of 2 mg/lb. body weight heparin (Roche) and the needles were then connected by 1.5 mm bore polythene tubing to a pH-measuring apparatus (fig. 1) so that a continuous measurement of arterial blood pH could be made, using a Pye "Master" pH meter. Side arms in the polythene tubing near the arterial and venous needles were used for blood sampling and the administration of intravenous injections. At the end of an experiment, protamine sulphate was administered in order to restore normal blood coagulation. Anaesthesia was induced by the intravenous injection of thiopentone sodium (Intraval Sodium) and the dog was intubated with a cuffed Magill tube. The appropriate anaesthetic vapour was then administered from a Boyle's apparatus, using a Water's attachment, with an 8-oz. soda lime canister, and a 1-gallon rebreathing bag.

Blood samples were taken directly under oil, and 0.1 ml samples were then immediately withdrawn for estimation of the total blood carbon dioxide by the method of Conway (1947). The

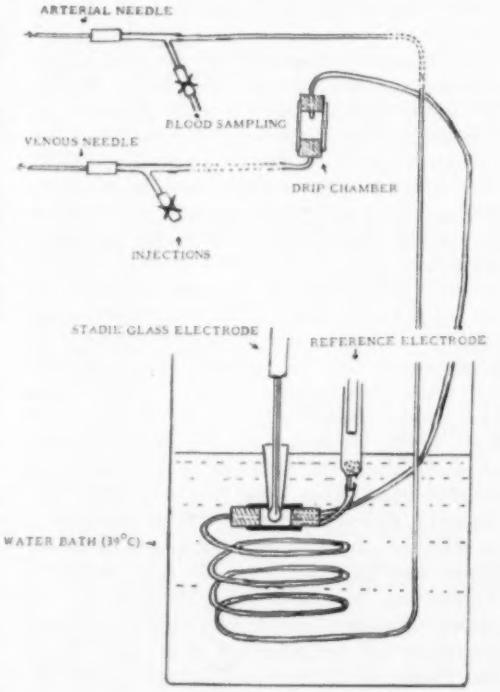


FIG. 1

Apparatus for the measurement of arterial blood pH, and the sites used for blood sampling and the administration of intravenous injections.

blood sample was then centrifuged and the plasma decanted for electrolyte estimations.

Potassium and sodium were estimated with an EEL flame photometer, using suitable dilutions of a standard solution as a reference. Calcium and magnesium were estimated by precipitation as oxalate and magnesium ammonium phosphate respectively, the precipitates being redissolved in nitric acid and titrated with 0.001N EDTA, using an ethanolamine buffer, pH 10.4 and solochrome black as an indicator.

Plasma inorganic phosphate was estimated by a modification of the method of Simonsen, Westover and Wertman (1947).

EXPERIMENTAL RESULTS

Control experiments.

In order to determine the changes which might occur in the blood electrolytes in a conscious dog, three experiments were carried out in which anaesthesia was not induced. Blood samples were taken every 30 minutes for a period of 2 hours. The results which were obtained in these experiments are shown in figure 2, which indicates the changes which occurred from the control concentrations. These results indicated that although minor changes in concentration might occur, there was no consistent trend.

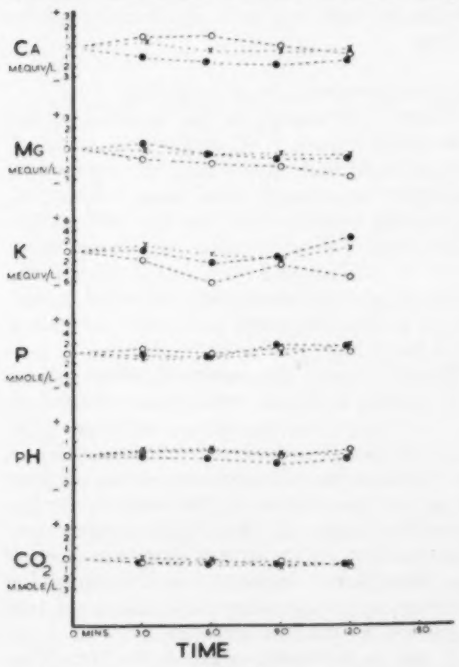


FIG. 2

Premedication only, showing the results of three experiments and indicating variations from the control blood sample taken at 0 minutes.

Thiopentone-ether anaesthesia.

In these and subsequent experiments a control blood sample was taken immediately prior to the induction of anaesthesia. Anaesthesia was induced with just sufficient thiopentone sodium to allow endotracheal intubation and was then deepened to the plane of surgical anaesthesia with ether and oxygen at a flow rate of 4 litres per minute. The results which were obtained in three 2-hour experiments are shown in figure 3.

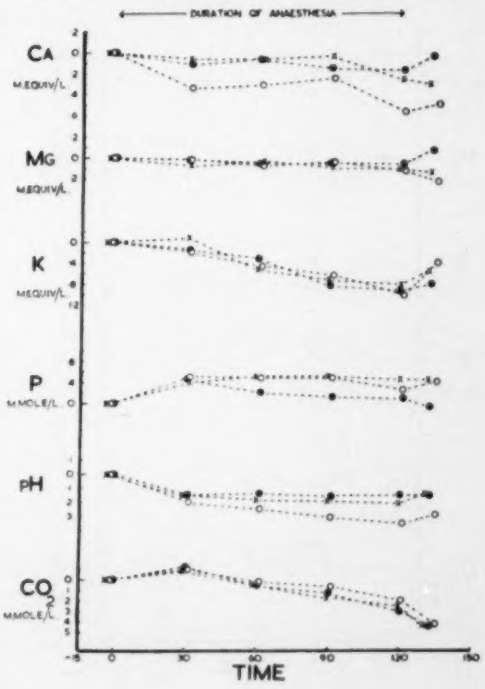


FIG. 3

Thiopentone-ether anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

The potassium concentration showed a gradual decrease, the progressive nature of which was in contrast to the changes in concentration of the plasma inorganic phosphate and the blood pH, which were greatest during the first 30 minutes of anaesthesia. The initial increase, followed by a gradual decrease, in the total carbon dioxide content of arterial blood indicated that the depth of anaesthesia might determine the presence or absence of respiratory acidosis during ether anaesthesia in the dog, since it was found difficult to maintain a plane of surgical anaesthesia during the second hour of experimentation. Dripps and Severinghaus (1955) pointed out that most earlier workers had found both a metabolic and respiratory acidosis, whereas recent workers have usually only reported a metabolic acidosis.

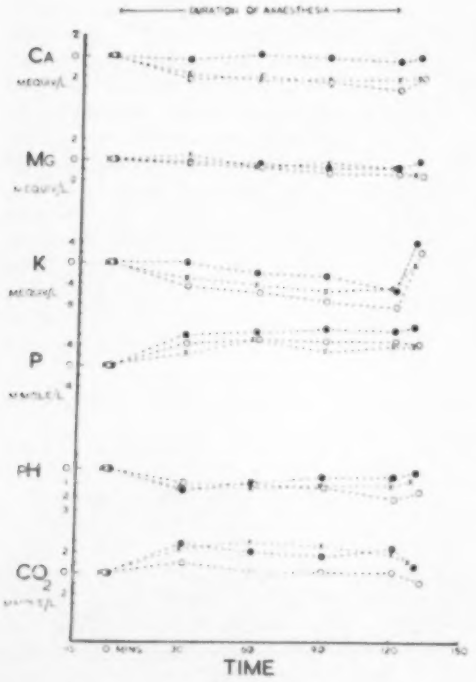


FIG. 4

Thiopentone-cyclopropane anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

These results show good agreement with most previous reports. There seems little evidence for a consistent decrease in the plasma concentrations of calcium and magnesium. No significant changes in the sodium concentration, as determined by the flame photometer, were found in these and other experiments in this investigation.

Thiopentone-cyclopropane anaesthesia.

In these experiments thiopentone was again used for the induction of anaesthesia prior to intubation and the administration of cyclopropane. A gas flow rate of 4 litres per minute of oxygen was used in order to minimize the possibility of carbon dioxide retention.

The results of three experiments are shown in figure 4. The chief difference between ether and cyclopropane was shown in the changes in the carbon dioxide content of arterial blood. With cyclopropane the decrease in pH could almost entirely be explained by the increase in carbon dioxide and there was not a significant metabolic acidosis.

Thiopentone-nitrous oxide anaesthesia.

Induction of anaesthesia was achieved by the intravenous injection of thiopentone in larger amounts than were used during the experiments with ether and cyclopropane, since it is difficult to maintain anaesthesia in the dog with nitrous oxide alone. For this reason, too, further injections of thiopentone were given during the course of an experiment when necessary. A flow rate of 2 litres of oxygen and 6 litres of nitrous oxide per minute were used.

Figure 5 shows the results obtained in three experiments. Small but well-defined changes in the electrolyte concentrations were found. The most significant of these were the depression of the potassium and the elevation of the inorganic phosphate concentrations, the greatest changes occurring during the first hour of anaesthesia. The elevation of the carbon dioxide content of the blood largely depended on the amount of thiopentone used, since this influenced the degree of respiratory depression.

It was found that in some cases, where thiopentone had been given by a rapid initial injection of most of the dose ultimately required, there was a transient increase in the pH of the

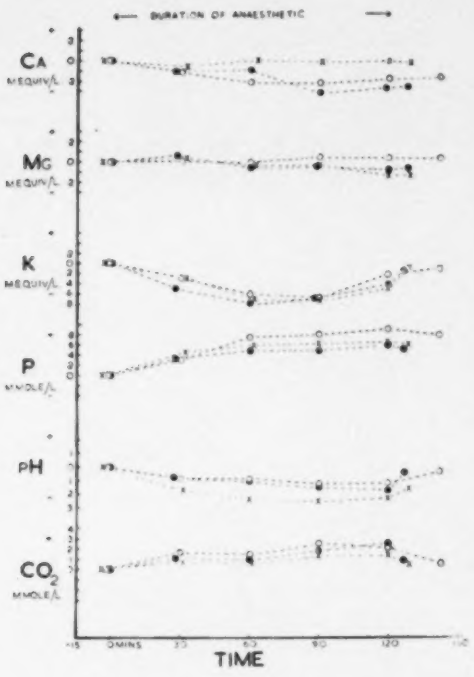


FIG. 5

Thiopentone-nitrous oxide anaesthesia. Three experiments showing the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

blood. This was unexpected and, since the rise was never more than 0.02 pH units, it was at first thought that this was due to a slight drift in the pH meter. However, it was also noted that the increase always coincided with a period of apnoea and that the pH had always returned to the control value, or below, by the time respiratory movements recommenced. It was also found that this change could be reproduced with regularity provided a sufficient amount of thiopentone was given by rapid injection. Further experiments were undertaken which indicated that the increase in pH was not due to the alkalinity of the thiopentone solution or to changes in the buffering capacity of the blood due to a decreased oxygen tension. At present no satisfactory explanation can be given for this phenomenon.

Hydroxydione-nitrous oxide anaesthesia.

The results of two experiments using these agents are shown in figure 6. It was found that dogs required up to 100 mg of hydroxydione sodium (Viadril) per kg body weight and since this drug must be given as a dilute solution, owing to the danger of thrombosis, the amount of injection necessary to produce even light narcosis was too large to be clinically practical in this species. The results obtained showed that there was little change in the blood pH or carbon dioxide content, although the latter was slightly reduced at the end of 2 hours anaesthesia. The only significant change was that of the potassium concentration, which showed the decrease commonly associated with anaesthesia.

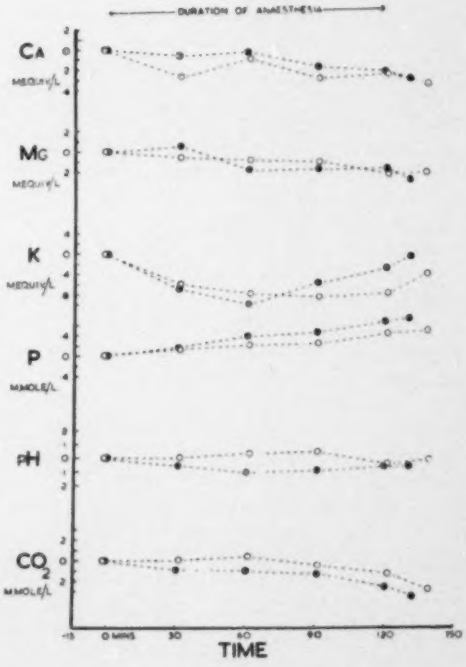


FIG. 6

Hydroxidione-nitrous oxide anaesthesia. Two experiments indicating the variations from the control concentrations found prior to the induction of anaesthesia at 0 minutes.

The effect of carbon dioxide retention during anaesthesia with thiopentone and nitrous oxide.

The inadvertent retention of carbon dioxide has often been blamed for the occurrence of anaesthetic emergencies. Although there have been many reports indicating that respiratory acidosis may occur during clinical anaesthesia in man (Dripps and Severinghaus, 1955), these mainly refer to the use of cyclopropane in closed circuit. There are no reports in the veterinary literature which indicate that respiratory acidosis is a clinical problem, even when pentobarbitone is used as an anaesthetic agent.

The following experiments were, therefore, of interest both to determine the electrolyte changes which might occur during respiratory acidosis and the degree of this which might be found during clinical anaesthesia in this species, using standard medical anaesthetic equipment.

In order to produce carbon dioxide retention, the soda lime canister was omitted from the anaesthetic circuit and the gas flow rate was reduced. A flow rate of 1 litre of oxygen and 1 litre of nitrous oxide per minute was used for the first 20 minutes but at this flow rate the pH never fell by more than 0.3 pH units. In order to produce more severe changes it was necessary to reduce the total gas flow rate to 100 ml of oxygen per minute. At the end of 2 hours anaesthesia the decrease in pH was 0.6—0.8 pH units. It therefore seems unlikely that severe respiratory acidosis may occur during anaesthesia in dogs, when standard medical equipment and the usual total gas flow rates are used.

Figure 7 shows the results obtained in two experiments carried out on the same dog. In the experiment the results of which are plotted by black circles the respiration became very distressed and the degree of carbon dioxide retention was therefore limited. In the other experiment the respiration was depressed when necessary by the injection of small amounts of thiopentone. In the first of these experiments the plasma potassium concentration started to increase earlier and also rose higher by the end of the second hour of anaesthesia than in the second experiment. Although there was a marked difference between the carbon dioxide content of the blood in these two experiments,

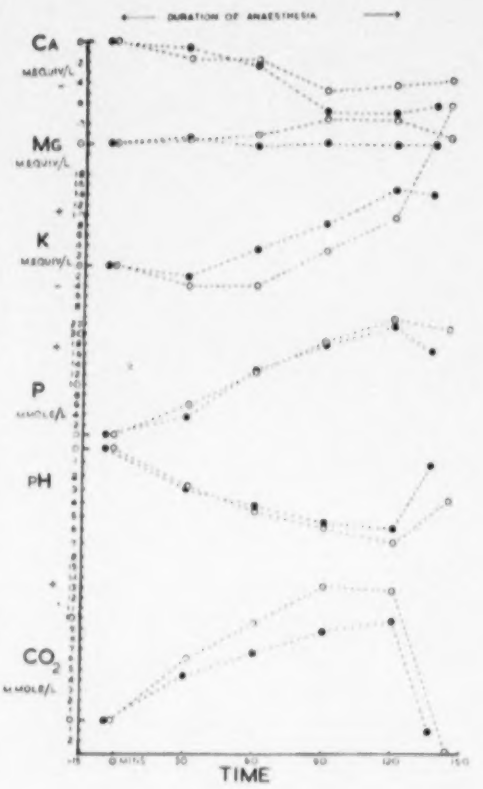


FIG. 7

Thiopentone-nitrous oxide anaesthesia. Two carbon dioxide retention experiments carried out on the same dog. Time in minutes from the induction of anaesthesia.

the fall in pH was very similar. This suggested that there was a greater degree of metabolic acidosis in the first of these experiments.

The plasma calcium concentration had fallen by the end of both these experiments but there was no significant change in the magnesium concentration. The plasma inorganic phosphate concentration was about twice the control concentration by the end of the second hour of anaesthesia.

Since it seemed likely from these experiments that the degree of metabolic acidosis and the increase in potassium concentration might be

related to the degree of respiratory distress, further experiments were carried out to test this theory. Unfortunately in all the other dogs used the respiration never became really distressed although the rate and depth of respiration did show a considerable increase. The results of three such experiments are shown in figure 8 which indicates that a large depression of arterial blood pH can be attained without causing a significant rise in the potassium concentration above the control value.

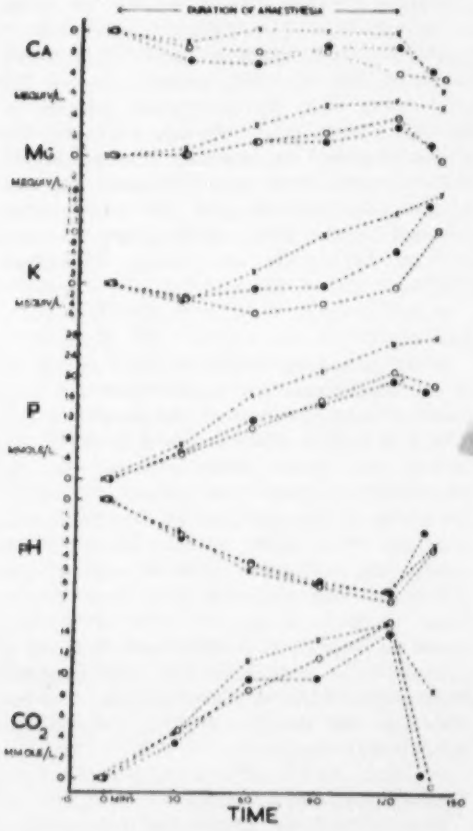


FIG. 8

Thiopentone-nitrous oxide anaesthesia. Three experiments involving the retention of carbon dioxide. Induction of anaesthesia was at 0 minutes.

DISCUSSION

Calcium and magnesium.

The results obtained in this investigation confirm those of other workers who had reported a slight, but inconsistent, decrease in the plasma calcium concentration (Eisler, Geness and Dienerstein, 1929; Lipow, Weaver and Reed, 1929). The plasma magnesium concentration was found to be very stable and it is possible that the variable results of previous investigations may have been due to the methods of estimation.

Plasma inorganic phosphate.

The changes in this ion which have been found during the present investigation agree well with those which have already been reported. Large changes in the plasma inorganic phosphate concentration have been found during respiratory acidosis and alkalosis and this suggests that the main factor concerned in producing changes in concentration is the pH of the blood, as was first suggested by Magee, Anderson and Glennie (1928). This does not necessarily contradict the belief of Foldes, Murphy and Wilson (1950) and Henneman and Vandam (1957) that anaesthetic agents per se may affect the plasma inorganic phosphate as a result of an effect on carbohydrate metabolism, but suggests rather that carbon dioxide tension may be more active in this respect. Whether the plasma concentration of this ion could be used as a measure of respiratory acidosis is doubtful, since in the dog other factors, such as shock, may also cause an increase (Wiggers, 1950).

Potassium.

The plasma potassium concentration appears to be more labile than that of the other blood electrolytes which have been studied. Unless frequent blood samples are taken it may be difficult to assess changes in concentration with accuracy.

This investigation has confirmed the fact that the potassium concentration is decreased by anaesthesia to a degree depending to some extent on the anaesthetic agent used. Thus the decrease during the first hour of anaesthesia was greater when hydroxydione or thiopentone and

nitrous oxide was used than during the use of ether or cyclopropane.

The significance of the decrease in potassium concentration during anaesthesia is not fully known but it seems likely that potassium tends to enter tissue cells due to changes in metabolism. Removal of the kidneys does not affect the fall caused by ether anaesthesia (Gerschman and Marenzi 1933a, b). Larson and Brewer (1939), however, were able to prevent this fall by the administration of 2, 4 dinitrophenol which is now known to uncouple cellular oxidative processes and phosphorylation. Brewster, Bunker and Beecher (1952) believed that the decrease in plasma potassium concentration during ether anaesthesia was of a similar order to that found during prolonged infusion of adrenaline. They found that the fall did not occur when dogs were given a high epidural nerve block prior to the induction of ether anaesthesia. It must be noted, however, that Larson and Brewer (1939) still found a decrease in potassium concentration in adrenal medullectomized dogs, but the method of adrenal medullectomy used by these workers was not described.

Carbon dioxide retention has been found to be associated with an increased potassium concentration in the plasma by the end of the second hour of anaesthesia, but this investigation has shown clearly that it is possible to have a severe respiratory acidosis without an increase above the control concentration. The increase in concentration previously reported by workers such as Sealy, Young and Harris (1954) and Brown (1955) is misleading, since their control samples were always taken after the induction of anaesthesia with thiopentone or pentobarbitone, agents which produce a large decrease in potassium concentration within a few minutes of induction of anaesthesia.

It is possible that there is a threshold concentration of carbon dioxide in the inspired gases above which the potassium concentration of the plasma becomes increased. Such thresholds have already been shown for the stimulation of the adrenal medulla and cortex and the release of potassium from the liver by carbon dioxide (Fenn and Asano, 1956; Tenney, 1956; Richards and Stein, 1957). From the results obtained in this investigation it seems possible that the threshold for the increase in plasma potassium concentration may be affected by the depth of anaesthesia. It must be emphasized that the severity of any changes which may be found is dependent on the length of time for which retention has occurred as well as on the prevailing carbon dioxide tension.

The rise in the plasma potassium concentration which is often found when the carbon dioxide tension in the inspired gases is returned to normal after the administration of high concentrations was thought by Sealy, Young and Harris (1954) to be due to the reflex release of adrenaline, for they showed that this rise could be prevented by the prior administration of piperoxane, an adrenolytic agent. This theory cannot be fully accepted, however, since it has been found that the intravenous infusion of adrenaline causes only a transient increase in the plasma potassium concentration (Brewer, Larson and Schroeder, 1939) and piperoxane does not inhibit this transient rise in concentration, although frequent blood sampling may be necessary to demonstrate its presence (Stevenson, 1959).

Sodium.

Although sodium estimations were carried out in all experiments, the results have not been included since no consistent changes were found. This is of interest, since Arends et al. (1952) and Billings and Brown (1955) reported that the administration of high concentrations of carbon dioxide in the inspired gases of dogs produced a reduction of about 20 per cent in the plasma volume and it therefore might be expected that the plasma sodium concentration would change. Since Giebisch, Berger and Pitts (1955) have found an increase in concentration of up to 10 m.equiv/l. in nephrectomized dogs inspiring high concentrations of carbon dioxide, it is possible that the kidney may have a homeostatic effect in this respect.

Hydrogen-ion concentration.

It is believed that the present investigation is the first in which continuous measurement of the arterial pH has been carried out in conscious dogs. Methods for the continuous recording of pH in acute experiments have been used by

Bjurstedt (1946), Hesser (1949) and Aström (1952).

It is evident from the results of this study and from those already reported in the literature (Dripps and Severinghaus, 1955), that the changes which are found in the arterial blood pH of the dogs during anaesthesia, especially when respiratory acidosis or alkalosis is present, are much greater than those found in man.

The decrease in the blood pH which has been found with increasing concentrations of carbon dioxide in this investigation closely corresponds with the changes which have been previously reported by Spencer et al. (1950), Joels and Samueloff (1956), Mollaret, Pocidalo and Lissac (1956) and Lissac et al. (1958) in dog experiments.

Carbon dioxide.

There has been a tendency to blame changes in the carbon dioxide tension as well as disturbances in "electrolyte balance" for many of the untoward events which may occur during anaesthesia.

While it is true that very high arterial tensions of carbon dioxide have been reported during anaesthesia in man (Dripps and Severinghaus, 1955), by no means all these reports have related to patients who had subsequently died. In most instances the anaesthetic has been cyclopropane, given by closed circuit methods. Where nitrous oxide is used in veterinary anaesthesia it is general practice to use a minimum gas flow rate of 2 to 4 litres per minute even when respiration is controlled and it seems unlikely that serious carbon dioxide retention will occur with this technique even when the soda lime becomes exhausted.

It has been found that recovery from anaesthesia in the dog which has been accompanied by severe carbon dioxide retention may not necessarily be prolonged. Indeed, since carbon dioxide may reduce the amount of thiopentone necessary to maintain a given plane of anaesthesia (Brodie and Hogben, 1957), recovery may be more rapid than usual when the carbon dioxide tension is returned to normal values and anaesthesia terminated. This does not mean that carbon dioxide may be regarded as an aid to anaesthesia but it does confirm the belief of Dripps and Severinghaus (1955) that experimental animals, including dogs, may be able to withstand the effects of prolonged carbon dioxide retention, provided that the pH is not allowed to change too rapidly at the termination of retention, without showing serious side effects.

It must be emphasized that this experimental work was carried out on healthy animals and that the results obtained do not indicate to what degree carbon dioxide retention will affect the metabolic responses of a diseased animal. It is also evident that the length of time for which carbon dioxide is retained is as important as the degree of respiratory acidosis which may be present, in determining the severity of metabolic responses.

SUMMARY

Anaesthesia induced by thiopentone sodium and maintained by ether, cyclopropane or nitrous oxide, produces little change in the total plasma calcium and magnesium concentrations. If respiratory acidosis is severe, the calcium concentration falls either during or shortly after recovery from anaesthesia.

The plasma potassium concentration falls during anaesthesia, although the changes may be only slight during anaesthesia maintained by ether or cyclopropane. No significant change has been noted in the plasma sodium concentration.

The changes in plasma inorganic phosphate are similar in nature to those of the hydrogen-ion concentration.

Except in ether anaesthesia there is an increase in the total blood carbon dioxide content and hydrogen-ion concentration during anaesthesia. In the case of ether anaesthesia the carbon dioxide content of the blood is ultimately reduced although the hydrogen-ion concentration still shows an increase.

ACKNOWLEDGMENTS

This work was carried out during the tenure of a May & Baker Research Fellowship. May & Baker Ltd., also generously provided a pH meter and drugs. Technical assistance was provided by Miss B. A. Sheppard. The advice and criticism of Dr. L. W. Hall, and Mr. A. A. Wilson, is gratefully acknowledged.

REFERENCES

Agnoli, R. (1929). Studi sul magnesio 3: Influenzi die narcotici sulla magnesiemia. *Boll. Soc. ital. Biol. sper.*, **4**, 579.

Andrews, E., Petersen, W. F., and Klein, R. I. (1930). Calcium changes in the brain in ether anaesthesia. *Ann. Surg.*, **92**, 993.

Arends, R. L., Chambers, C. J., Draper, N. B., and Whitehead, R. W. (1952). Effect of diffusion respiration and of the inhalation of high concentrations of CO_2 on plasma volume, thiocyanate space, blood cells and O_2 capacity. *Amer. J. Physiol.*, **171**, 507.

Aström, A. (1952). On the action of combined carbon dioxide excess and oxygen deficiency in the regulation of breathing. *Acta Physiol scand.*, **27**, suppl. 98.

Billings, H. H., and Brown, E. B. jr. (1955). Effect of splenectomy on changes in plasma and blood volume produced by inhalation of 30 per cent and 40 per cent CO_2 in dogs. *Amer. J. Physiol.*, **180**, 363.

Bjurstedt, A. G. H. (1946). Interaction of centrogenic and chemoreflex control of breathing during oxygen deficiency. *Acta Physiol. scand.*, **12**, suppl. 38.

Bolliger, A. (1926). Phosphate metabolism as related to anaesthesia. *J. Biol. Chem.*, **69**, 721.

Brauchli, E., and Schnider, O. (1929). Über die ionenverschiebungen im blut bei narcose- und erregungszuständen. *Arch. exp. Path. Pharmak.*, **119**, 240.

Brewer, G., Larson, P. S., and Shroeder, A. B. (1939). On the effect of epinephrine on blood potassium. *Amer. J. Physiol.*, **126**, 708.

Brewster, W. R., Bunker, J. P., and Beecher, H. K. (1952). Metabolic effects on anesthesia. 4: Mechanism of metabolic acidosis during ether anesthesia in the dog. *Amer. J. Physiol.*, **171**, 37.

Brodie, B. B., and Hogben, C. A. M. (1957). Some physio-chemical factors in drug action. *J. Pharm. Lond.*, **9**, 345.

Brown, E. B. jr. (1955). Role of hyperkalemia in the production of ventricular fibrillation following hypercapnia. *Proc. Soc. exp. Biol., N.Y.*, **90**, 319.

—— Prasad, A. S. (1957). Plasma ultrafiltrable calcium concentration in posthypercapnic ventricular fibrillation. *Amer. J. Physiol.*, **190**, 462.

Cloetta, M., and Thomann, H. (1924). Chemisch-physikalische untersuchungen zur theorie der narcose. *Arch. exp. Path. Pharmak.*, **103**, 260.

—— Fischer, H., and van der Loeff, M. R. (1934). Die biochemie von schlaf und erregung mit bisonderer berücksichtigung der bedeutung der kationen. *Arch. exp. Path. Pharmak.*, **174**, 589.

—— —— —— (1942). Die verteilung und die wirkung des magnesiums im organismus und deren beeinflussung durch calcium. *Arch. exp. Path. Pharmak.*, **200**, 6.

Conway, E. J. (1947). *Microdiffusion Analysis and Volumetric Error*, 2nd ed. London: Crosby Lockwood.

Dripps, R. D., and Severinghaus, J. W. (1955). General anaesthesia and respiration. *Physiol. Rev.*, **35**, 741.

Eisler, B., Geness, S., and Dienerstein, S. (1929). Über den einfluss der narcose auf den elektrolytgehalt des serums. *Ber. ges. Physiol.*, **54**, 685.

Emerson, W. C. (1928). The effect of ether anaesthesia and shock on the calcium of the blood. *J. Lab. Clin. Med.*, **14**, 195.

Fay, M., Andersch, M., and Kenyon, M. B. (1939a). Blood studies under anaesthesia. 1: Ether administered to the dog by open drop and in a closed systems. *J. Pharmacol.*, **66**, 224.

—— —— —— (1939b). Blood studies under anesthesia. 2: Cyclopropane and ethyl ether. *J. Pharmacol.*, **66**, 234.

Fenn, W. O., and Asano, T. (1956). The effects of carbon dioxide inhalation on potassium release from the liver. *Amer. J. Physiol.*, **185**, 567.

Foldes, F. F., Murphy, A. J., and Wilson, B. C. (1950). The effect of various anaesthetic agents on inorganic serum phosphate levels. *J. Pharmacol.*, **100**, 14.

Gerschman, R., and Marenzi, A. D. (1933a). Action des anesthésiques sur le potassium du plasma sanguin. *C.R. Soc. Biol., Paris*, **112**, 508.

—— —— (1933b). Variations du potassium du plasma et due sang pendant l'anesthésie par l'éther. *C.R. Soc. Biol., Paris*, **112**, 509.

Giebisch, G., Berger, L., and Pitts, R. F. (1955). The extrarenal response to acute acid-base disturbances of respiratory origin. *J. clin. Invest.*, **34**, 231.

Henneman, D. H., and Vandam, L. D. (1957). Alterations in phosphate metabolism during general anaesthesia in man. *J. clin. Invest.*, **36**, 898.

Hesser, C. M. (1949). Central and chemoreflex components in the respiratory activity during acid-base displacements in the blood. *Acta Physiol. scand.*, **18**, suppl. 64.

Joels, N., and Samueloff, M. (1956). Metabolic acidosis in diffusion respiration. *J. Physiol.*, **133**, 347.

Larson, P. S., and Brewer, G. (1939). On the mechanism of the depression of serum potassium by anesthesia. *J. Pharmacol.*, **67**, 147.

Lipow, E., Weaver, W. K., and Reed, C. I. (1929). Effects of ether anesthesia on the inorganic constituents of the blood. *Amer. J. Physiol.*, **90**, 432.

Lissac, J., Pocidalo, J. J., Finetti, P., and Liot, F. (1958). Modifications des cations plasmatiques au cours de l'hyperventilation aiguë chez le chien. *C.R. Soc. Biol., Paris*, **151**, 2068.

Magee, H. E., Anderson, W., and Glennie, A. E. (1928). Some observations on the effect of ether anaesthesia on the composition of the blood and their relation to thyroid function. *Brit. J. exp. Path.*, **9**, 119.

Marenzi, A. D., and Gerschman, R. (1933). Variations des éléments minéraux du plasma pendant l'anesthésie éthérée. *C.R. Soc. Biol., Paris*, **114**, 1226.

Mollaret, P., Pocidalo, J. J., Lissac, J., and Demongeot, C. (1956). Modifications humorales, circulatories et electrocardiographiques au cours de l'acidose respiratoire aiguë chez le chien soumis à la respiration dite diffusion. *C.R. Soc. Biol., Paris*, **150**, 2168.

Potter, D. G. E. (1925). Changes in the blood in anaesthesia. *Quart. J. Med.*, **18**, 261.

Prasad, A. S., Flink, E. B., and Brown, E. B. jr. (1957). Plasma ultrafiltrable magnesium in respiratory alkalosis and acidosis. *Proc. Soc. exp. Biol., N.Y.*, **96**, 629.

Richards, J. B., and Stein, S. N. (1957). The effect of CO_2 exposure and respiratory acidosis on adrenal 17-hydroxycorticosteroid secretion in anaesthetized dogs. *Amer. J. Physiol.*, **188**, 1.

Robbins, B. H., and Pratt, H. A. (1936). Ether anesthesia: changes in the serum potassium content during and following anaesthesia. *J. Pharmacol.*, **56**, 205.

Sealy, W. C., Young, W. G., and Harris, J. S. (1954). Studies on cardiac arrest: the relationship of of hypercapnia to ventricular fibrillation. *J. thorac. Surg.*, **28**, 447.

Simonsen, D. G., Westover, L. M., and Wertman, M. (1947). The determination of serum magnesium by the molybdivanadate method for phosphate. *J. Biol. Chem.*, **169**, 39.

Spencer, J. N., Parry, T. M., Whitehead, R. W., and Draper, W. B. (1950). The tolerance of the dog under thiopental sodium anaesthesia to high concentrations of carbon dioxide. *J. Pharmacol.*, **98**, 366.

Stehle, R. L., and Bourne, W. (1924). Concerning the mechanism of acidosis in anesthesia. *J. Biol. Chem.*, **60**, 341.

Stevenson, D. E. (1959). A study of changes in the blood electrolytes of the dog caused by anaesthesia. Ph. D. Thesis, University of Cambridge.

Tenney, S. M. (1956). Sympatho-adrenal stimulation by carbon dioxide and the inhibitory effect of carbonic acid on epinephrine response. *Amer. J. Physiol.*, **187**, 341.

Waters, R., and Schmidt, E. (1934). Cyclopropane anesthesia. *J. Amer. med. Ass.*, **103**, 975.

Wiggers, C. J. (1950). *Physiology of Shock*. New York: The Commonwealth Fund.

WAIKATO HOSPITAL BOARD, HAMILTON, NEW ZEALAND

ANAESTHETIST

Applications are invited from suitably qualified Medical Practitioners possessing a Postgraduate Diploma in Anaesthesia, for the position of wholetime Anaesthetist at Waikato Hospital, Hamilton, New Zealand.

Salary scale will be either: Senior Specialist—£NZ.2,100–2,400 or
Junior Specialist—£NZ.1,700–2,000.

The scale applicable to the appointee and the commencing rate within such scale will be determined in accordance with the provisions of the Hospital Employment (Medical Officers) Regulations based upon the experience and qualifications of the successful applicant.

Travelling expenses. Assistance in this regard is available and full details will be found in the Conditions of Appointment.

Conditions of Appointment and official application form are obtainable from the office of the HIGH COMMISSIONER FOR NEW ZEALAND, 415 STRAND, LONDON, W.C.2, and applications will close with the SECRETARY, WAIKATO HOSPITAL BOARD, P.O. BOX 934, HAMILTON, NEW ZEALAND, on TUESDAY, DECEMBER 6, 1960.

Brit. J. Anaesth. (1960), 32, 364

CHANGES IN THE BLOOD ELECTROLYTES OF ANAESTHETIZED DOGS CAUSED BY SUXAMETHONIUM

BY

D. E. STEVENSON

School of Veterinary Medicine, University of Cambridge, England

IN a previous paper (Stevenson, 1960) the changes in the blood electrolytes which may occur as a result of anaesthesia in dogs have been discussed. This paper describes how such changes may be modified by the use of suxamethonium chloride as a muscle relaxant during anaesthesia.

Perry and Zaimis (1954) showed that suxamethonium causes the release of potassium from perfused voluntary muscle, while Klupp, Kraupp, Honetz, Kobinger and Loudin (1954) demonstrated that in dogs depolarizing muscle relaxants, including suxamethonium, will cause an increase in the plasma potassium concentration which they claimed to be biphasic. These workers claimed that the potassium concentration could be restored to the normal value by the administration of d-tubocurarine subsequent to the injection of suxamethonium. Paton (1956) has shown in cats that the injection of suxamethonium will cause an increase in the plasma potassium concentration due to release from skeletal muscle which is associated with a partial depolarization of the muscle surface.

METHODS

The techniques used for investigation have already been described (Stevenson, 1959, 1960). In this series of experiments the rate of ventilation following suxamethonium-induced apnoea was controlled to keep the pH of arterial blood just below the pre-anaesthetic value.

The depolarization of skeletal muscle was measured by a similar method to that of Paton (1956). After the induction of anaesthesia a small skin incision was made on the lateral aspect of the quadriceps femoris muscle, and a silver-silver chloride nonpolarizable electrode was placed beneath the fascia of this muscle. A similar electrode was placed beneath the skin of the foot as a reference electrode. The potential difference between these electrodes was measured on a modified Pye "Master" pH meter.

Blood pressure recordings were made on a Cambridge Instrument Co. three-channel recorder, using an optical manometer. Blood-pressures were measured from the needle in the carotid loop.

EXPERIMENTAL RESULTS

Anaesthesia was induced by the administration of thiopentone sodium into the pH-recording blood circuit near the intravenous needle. The dog was then intubated and anaesthesia was maintained with nitrous oxide. When a satisfactory plane of anaesthesia was reached, suxamethonium chloride (Brevidil "M") was given by intravenous injection at a dose rate of about 0.3 mg/kg (total salt). This dose rate was just sufficient to paralyze diaphragmatic respiration and usually produced apnoea of 10 to 15 minutes duration. Further injections of suxamethonium were given whenever there were signs of returning respiratory movements. During the course of apnoea, artificial respiration was maintained by rhythmical compression of the rebreathing bag. The rate of ventilation was adjusted so that a steady blood pH was maintained.

The results of three experiments are shown in figure 1, and confirm the minimal metabolic effects which are normally produced by suxamethonium. Since the blood pH was maintained just below the control value, the carbon dioxide content of the arterial blood was somewhat less than had been found with nitrous oxide anaesthesia alone (Stevenson, 1960). It was interesting

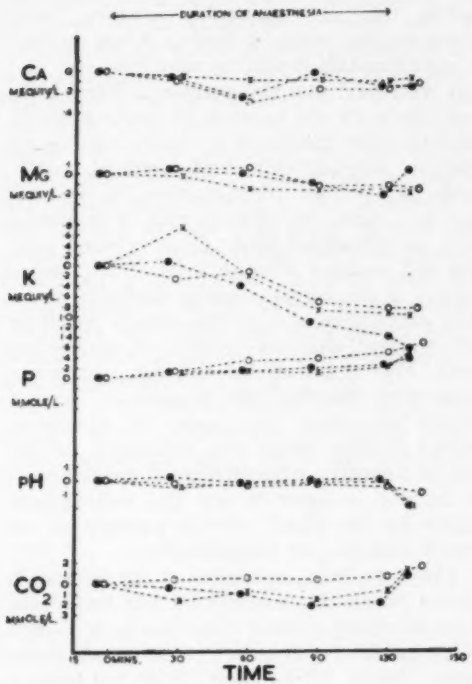


FIG. 1

Thiopentone-nitrous oxide anaesthesia. The effects of muscle relaxation produced by the administration of suxamethonium to three dogs. The graph indicates changes from the control concentrations prior to the induction of anaesthesia.

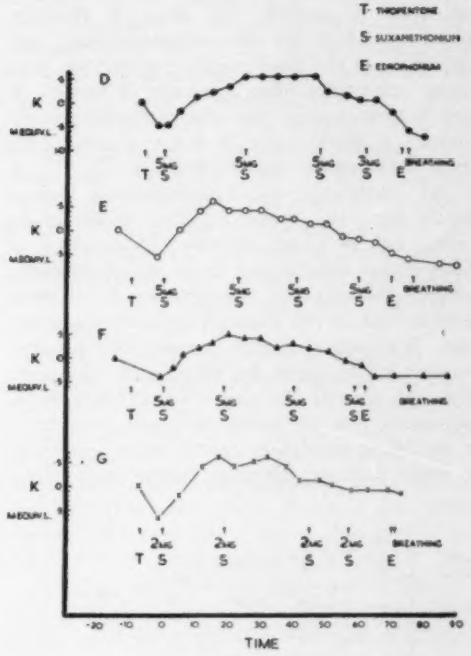


FIG. 2

The effect of suxamethonium (0.3 mg/kg) on the plasma potassium concentrations of four dogs anaesthetized with thiopentone and nitrous oxide. The first injection of suxamethonium was made at 0 minutes, the control blood samples being taken prior to the induction of anaesthesia.

to note that in this case there was very little change in the plasma inorganic phosphate concentration. No significant changes in sodium concentration were found in any experiment.

The changes found in the potassium concentration were unexpected. The work of Klupp et al. (1954) and of Paton (1956) indicated that a rise in the plasma concentration should be found following the injection of suxamethonium. The most obvious effect, however, was a fall in concentration during the second hour of anaesthesia, sometimes by over 25 per cent of the control concentration. This decrease was still evident when the final blood sample was taken, unlike the decrease in potassium concentration encountered during anaesthesia when muscle relaxants were not used.

In order to clarify the changes in the potassium concentration occurring during the first hour of anaesthesia, further experiments were carried out employing more frequent blood sampling. The results of four experiments are shown in figure 2. It was now found that the potassium concentration increased after the first injection of suxamethonium, reaching a peak within 10 to 20 minutes and thereafter slowly declining until, 60 to 70 minutes after the first injection, a concentration was reached which approximated to that which would have been expected had no relaxant agent been given. No definite relationship appeared to exist between successive injections of suxamethonium and the plasma potassium concentration.

At this point in the investigation an attempt

was made to confirm the work of Hansson (1958) who believed that suxamethonium had little effect on the blood pressure of the dog, providing ventilation was adequate. However, it soon became evident that suxamethonium could produce a marked rise in blood pressure even when oxygenation was maintained (fig. 3). A second injection of suxamethonium given shortly after the initial injection produced no further rise in blood pressure. Examination of these results showed that there was a similarity between the effect of suxamethonium on blood pressure and on the plasma potassium concentration. It therefore seemed possible that suxamethonium might cause the release of adrenaline from the adrenal medulla, since D'Silva (1934) had shown that adrenaline can cause an increase in the blood potassium concentration as well as in blood pressure. Although further experiments

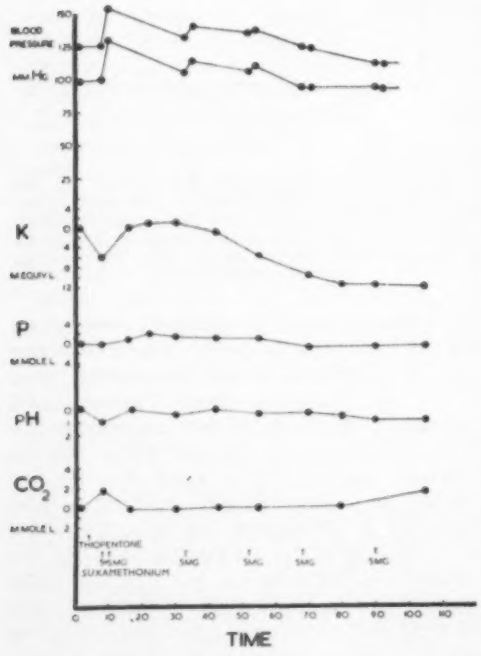


FIG. 3

The effect of suxamethonium on the blood pressure of an anaesthetized dog weighing 20 kg. Time in minutes from the control blood sample.

showed that the relationship between these factors was not always so marked, it was decided to investigate this possibility more fully.

It was found that the increase in blood pressure caused by the injection of suxamethonium could be either completely or nearly abolished by bilateral adrenalectomy, high epidural anaesthesia or by the administration of hexamethonium. After the administration of phentolamine, an adrenolytic agent, a rise in blood pressure still occurred although some of the characteristics of the normal response were lost. In all these experiments a rise in the plasma potassium still occurred after the injection of suxamethonium. This indicated that although suxamethonium may stimulate the sympathetic nervous system and cause the release of adrenaline, neither of these effects was responsible for the rise in potassium concentration. A further point of interest in figure 3 was the tachyphylaxis shown by the blood pressure response to repeated injections of suxamethonium.

The most likely explanation of the increase in plasma potassium concentration was that potassium was being released from muscle as a result of the partial depolarization of the muscle membrane (Zaimis, 1954). Paton (1956) had found a definite relationship between the degree of muscle depolarization and the plasma potassium concentration of cats following suxamethonium administration and he suggested (1959) that a similar type of investigation was worthy of a trial in dogs. Experiments were therefore carried out in which the depolarization of a leg muscle was recorded and urine was also collected at intervals in order to determine the urinary excretion of potassium.

The results of one such experiment are shown in figure 4. It is evident from these results that there is a relationship between the depolarization of muscle and the increase in the plasma potassium concentration. The peak depolarization potential was found to occur before the maximum rise in potassium concentration. Recordings from other muscle groups, however, may well yield different results.

After the first injection of suxamethonium, further injections temporarily altered the depolarization potential of the muscle. This usually tended to return to zero, that is if an injection

was given during the period of depolarization the degree of this was temporarily reduced, while if given during the period of hyperpolarization the degree of this was also reduced. Paton (1956) noted that in the cat the elevation of the plasma potassium concentration lasted considerably longer than the depolarization potential following an injection of suxamethonium. A similar relationship was also seen in this investigation and, together with the relationship between the peaks of these effects, affords evidence for the belief that potassium was released from the muscle following depolarization of the muscle membrane, rather than that the degree of depolarization was determined by the plasma potassium concentration.

Klupp et al. (1954) believed that if curare was injected after suxamethonium, the plasma potassium concentration would fall to the initial level and that further injections of suxamethonium would not cause an increase in potassium concentration until the curare was eliminated from the body. Examination of their results showed that the test doses of suxamethonium were given during a period when no rise in potassium would be seen, according to the present results, even if curare had not been given. It was therefore decided to re-examine the findings of these workers. Curare was considered unsuitable for this purpose, since it had been found to produce side-effects which might make the interpretation of the results obtained uncertain. Gallamine was therefore used.

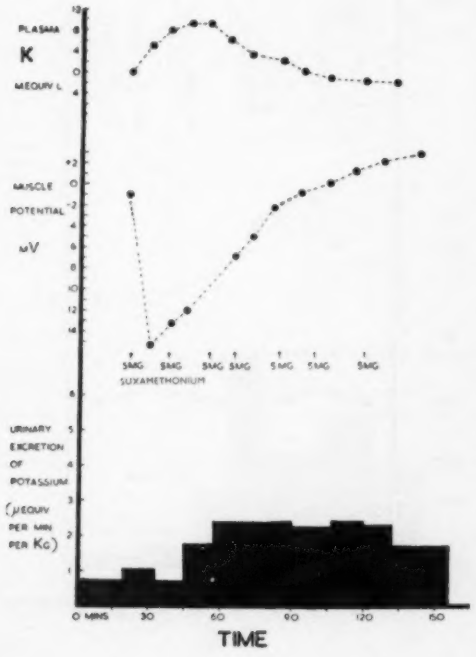


FIG. 4

The effect of suxamethonium on the plasma potassium concentration, polarization of muscle and the urinary excretion of potassium of an anaesthetized (16 kg) dog.

In this series of experiments gallamine was given after induction of anaesthesia by slow intravenous injection until the diaphragm was paralyzed. A further dose computed as half the paralyzing dose was then given. After a few minutes of controlled respiration, injections of suxamethonium were given at about the usual dose rate and frequency. The block produced by gallamine was never visibly antagonized. The results of one of these experiments are shown in figure 5. It must be noted that the control blood samples were taken after the induction of anaesthesia. This experiment showed that gallamine prevented the increase in the plasma potassium concentration caused by suxamethonium. Repeated injections of suxamethonium did, however, produce slight changes in the depolarization of muscle.

The results which have been obtained for the excretion rate of potassium in the urine are particularly interesting. They show that suxamethonium caused a prolonged increase in the excretion rate, even when the plasma potassium concentration remained stable as a result of the prior administration of gallamine. These results suggest that suxamethonium may have a direct action on the kidney. The similarity shown by Paton (1956) in cats between the plasma potassium concentration and the urinary excretion rate after the injection of suxamethonium was not evident in this investigation.

Muscle fasciculation, normally seen after the first injection of suxamethonium, was not seen in any experiments in which the injection of the drug was preceded by hexamethonium, phenactropinium or gallamine. It was seen, however, in

muscles which had been previously paralyzed by high epidural anaesthesia.

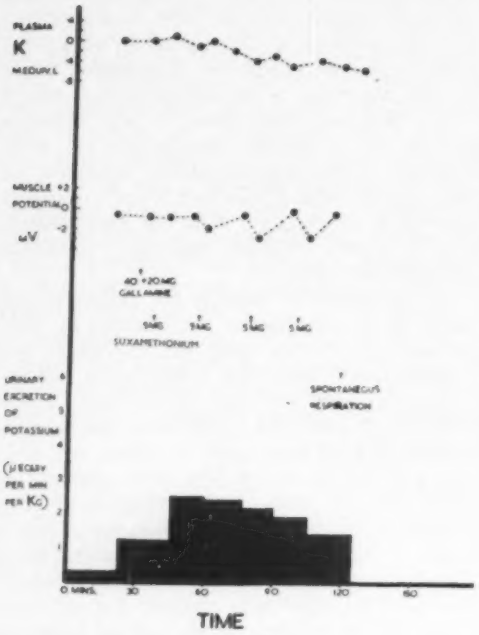


FIG. 5

The effect of the prior injection of gallamine on the changes in plasma potassium concentration, muscle polarization and urinary excretion of potassium caused by the administration of suxamethonium to an anaesthetized dog weighing 20 kg. The first blood sample was taken after induction of anaesthesia.

SUCCINYLMONOCHOLINE

Suxamethonium is metabolized to succinylmonocholine and then to succinic acid and choline (Bovet-Nitti, 1949; Whittaker, 1951). The first of these reactions is considered to be the more rapid (Lehmann and Silk, 1953). Since succinylmonocholine has been shown to have a weaker but more persistent blocking action than suxamethonium itself (Ellis, Wnuck, Fanelli and Beer, 1953), it has been postulated that accumulation of the monocholine may account for some cases of prolonged apnoea following the injection of suxamethonium in man (Bourne, Collier and Somers, 1952). A few experiments were therefore carried out to investigate the effects of succinylmonocholine during anaesthesia in the dog.

The effect of succinylmonocholine iodide on the blood pressure and the plasma potassium concentration is shown in figure 6. The increase in plasma potassium concentration was greater but more transient than that obtained with the dicholine compound. The effect on blood pressure confirms the statement of Paton (1953) who believed that the monocholine might produce an increase in blood pressure, but not the work of Ellis et al. (1953) who attributed a weak ganglionic blocking action to this compound. The

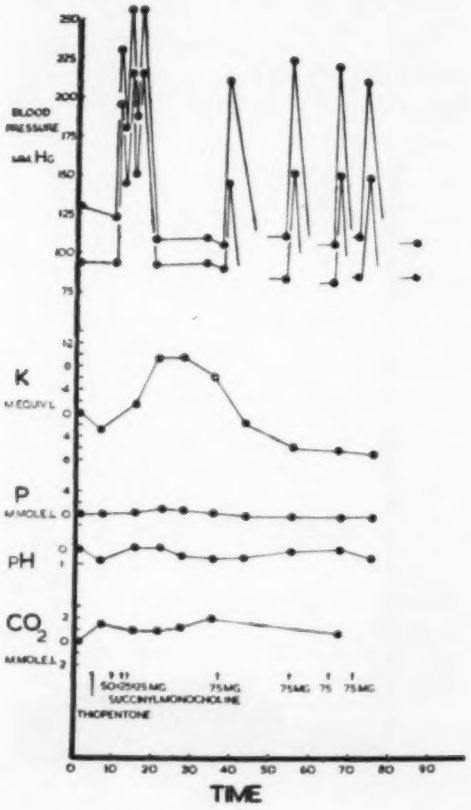


FIG. 6

The effect of succinylmonocholine on the blood pressure and the plasma potassium concentration of a 14 kg dog.

effect on blood pressure was perhaps more marked than with suxamethonium itself, but a larger amount of the monocholine compound had to be injected to inhibit respiration completely.

Respiratory paralysis appeared to develop more slowly than with the dicholine compound. It was also found that tachyphylaxis occurred and eventually it became difficult to inhibit completely voluntary respiratory movements by further injections of the drug. At this stage voluntary respiratory movements showed the inspiratory pause usually associated with partially curarized breathing. The effect on blood pressure, however, showed no sign of developing tachyphylaxis.

Since the dose of succinylmonocholine iodide required for complete paralysis of respiratory movements was at least twenty times that of suxamethonium, it seems unlikely that the former can be blamed for cases of prolonged apnoea in dogs. It is also of interest that the duration of apnoea following the injection of succinylmonocholine was much shorter than would have been expected if this compound is metabolized at a slower rate than suxamethonium itself. It seems likely that there is more than one route for the degradation of succinylmonocholine. It is possible that other tissues, such as the liver, may be capable of breaking down succinylmonocholine at a greater rate than that at which the dicholine is destroyed (Quastel, 1955).

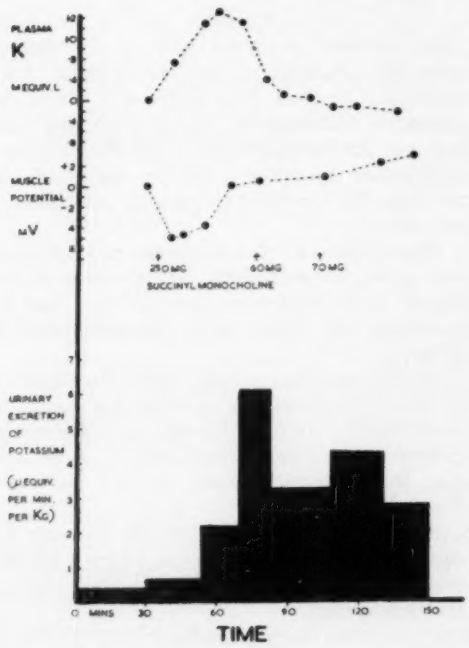


FIG. 7

The effects of succinylmonocholine on the plasma potassium concentration, muscle polarization and urinary excretion of potassium of a 16 kg dog. The first blood sample was taken after the induction of anaesthesia.

An experiment was carried out to assess the degree of muscle membrane depolarization caused by the injection of succinylmonocholine (fig. 7). The control blood sample was taken after the induction of anaesthesia. It may be seen that the depolarization potential was only about half the value usually obtained with suxamethonium and did not persist for the same length of time.

Only slight muscle fasciculations were noted after the intravenous administration of succinylmonocholine.

DISCUSSION

The development of a large decrease in the plasma potassium concentration by the prolonged administration of suxamethonium in dogs is of the greatest interest, since previous investigators have failed to demonstrate this phenomenon, although the initial increase had already been found in cats, dogs, horses and in man. The finding that the pattern of the plasma potassium concentration changes following the injection of suxamethonium in dogs was not altered by adrenalectomy, ganglionic blockade, adrenolytic drugs or high epidural anaesthesia confirms the belief of Paton (1956) that the increased potassium concentration results from the release of potassium from muscle rather than from sympathetic stimulation.

The double peak in the plasma potassium concentration which was described by Klupp et al. (1954) has not been confirmed in the present study.

The relationship between the peaks of the potassium concentration of the plasma and the

depolarization of muscle implies that the latter is the primary event. This is also implied by experiments in which gallamine was given prior to suxamethonium, since in this case successive injections of suxamethonium produced a progressive increase in the depolarization of muscle membrane without increasing the plasma potassium concentration.

It seems questionable in dogs whether there is in fact a close relationship between the degree of muscle depolarization and the development of neuromuscular block, since after prolonged administration of suxamethonium the latter was present without depolarization. This suggests that at this time suxamethonium may have become a pure nondepolarizing blocking agent. Further electrophysiological investigations are necessary to confirm this, but nevertheless there are many reports of anticholinesterase drugs reversing the actions of depolarizing drugs on both respiratory and leg muscles of dogs (Su, Kao and Karp, 1951; Zaimis, 1959; Foldes, 1959).

A period of hyperpolarization in cats was noted by Paton (1956) although in his results this did not develop until neuromuscular transmission had been restored. It seems doubtful whether this phenomenon can be explained by changes in the sodium distribution, for Malcolm and Paton (1951) were unable to demonstrate an increased uptake of Na^{24} by frog muscle in the presence of decamethonium. A study of figure 4 suggests that the phase of increased polarity may be due to the decreasing potassium concentration of the plasma, for if the muscle content of potassium was constant or increasing during this period an increase in the resting potential might be expected.

The effect which suxamethonium has been found to exert on the blood pressure of dogs is larger than had been previously reported. Hansson (1958) believed that any increase was secondary to hypoxia caused by respiratory depression. It was found in this study, however, that with the concentrations of oxygen normally used in the inspiratory gases respiratory movements could be completely inhibited without any increase in blood pressure. Furthermore no increase in blood pressure was seen when apnoea was induced by the administration of gallamine. Examination of Hansson's results showed that a rise in blood pressure was no longer produced if the dog was artificially respired when the last of several injections of suxamethonium was given. It is highly probable, therefore, that at this stage tachyphylaxis had developed and the use of artificial respiration was completely fortuitous.

The reports concerning the reversal of the effects of suxamethonium by anticholinesterase drugs have already been mentioned. In this study in every case following the administration of edrophonium or neostigmine after some degree of spontaneous respiratory movement had returned there was an immediate increase in the tidal volume. It seems reasonable in clinical practice to give these agents to dogs following the prolonged administration of suxamethonium when a satisfactory tidal volume does not develop.

SUMMARY

Suxamethonium produces a rise in the plasma potassium concentration of anaesthetized dogs which lasts for about 60 minutes, after which the potassium concentration falls steadily and also does not immediately recover following the termination of anaesthesia. During the whole of this time the urinary excretion of potassium is increased.

The changes in plasma potassium concentration are similar to changes in the resting potential of muscle and both these changes may be prevented by the prior administration of gallamine.

Succinylmonocholine also causes an elevation of the plasma potassium concentration lasting 30 to 40 minutes which is followed by a decrease in concentration. The depolarization of muscle is also more transient than is the case with suxamethonium.

Anticholinesterase drugs rapidly increase the depth of respiration when spontaneous respiratory movements reappears following suxamethonium apnoea.

ACKNOWLEDGMENTS

This work was carried out during the tenure of a May & Baker Research Fellowship. May & Baker Ltd. also provided generous supplies of drugs. Dr. A. C. White of Burroughs Wellcome Ltd. kindly provided a sample of succinylmonocholine. The author is grateful to Dr. L. W. Hall for advice, to Miss B. A. Sheppard for technical assistance, and to Miss J. Minns for help with the preparation of the figures.

REFERENCES

Bourne, J. G., Collier, H. O. J., and Somers, C. F. (1952). Succinylcholine (succinoylcholine), muscle relaxant of short duration. *Lancet*, **1**, 1225.

Bovet-Nitti, F. (1949). Degradazione di alcune sostanze curarizzanti per azione di colinesterase. *R.C. Ist. sup. Sanita.*, **12**, 138.

Ellis, C. H., Wnuck, A. L., Fanelli, R. V., and Beer, E. J. de (1953). Comparative pharmacological study of the mono and dicholine esters of succinic acid. *J. Pharmacol.*, **109**, 83.

Foldes, F. F. (1959), in Current concepts of the mode of action of depolarizing relaxants and their clinical implications. *Curare and curare-like Agents*, by Bovet, D., Bovet-Nitti, F., and Marini-Bettolo, G. B., p. 425. Amsterdam: Elsevier.

Hansson, C-H. (1958). Studies on the effect of succinylcholine in domestic animals. *Nord. Vetmed.*, **10**, 201.

Klupp, H., Kraupp, O., Honetz, N., Kobinger, W., and Loudin, M. (1954). Uber die freisetzung von kalium aus der muskulatur unter der einwirkung einiger muskelrelaxentien. *Arch. int. Pharmacodyn.*, **98**, 340.

Lehmann, H., and Silk, E. (1953). Succinylmonocholine. *Brit. med. J.*, **1**, 767.

Malcolm, J. L., and Paton, W. D. M., quoted by Burns, B. D., and Paton, W. D. M. (1951). Depolarization of the motor end-plate by decamethonium and acetylcholine. *J. Physiol.*, **115**, 41.

Paton, W. D. M. (1953). The principles of neuromuscular block. *Anaesthesia*, **8**, 151.

Paton, W. D. M. (1956). Mode of action of neuromuscular blocking agents. *Brit. J. Anaesth.*, **28**, 470.

—— (1959). Personal communication.

Perry, W. L. M., and Zaimis, E. J. (1954), quoted by Zaimis, E. J. (1954).

Quastel, J. H. (1955), quoted by R. Ottolenghi (1959). *Curare and Curare-like Agents*, by Bovet, D., Bovet-Nitti, F., and Marini-Bettolo, G. B., p. 442. Amsterdam: Elsevier.

D'Silva, J. L. (1934). The action of adrenaline on the serum potassium. *J. Physiol.*, **82**, 393.

Stevenson, D. E. (1959). A study of changes in the blood electrolytes of the dog caused by anaesthesia. Ph.D. Thesis, University of Cambridge.

—— (1960). Changes caused by anaesthesia in the blood electrolytes of the dog. *Brit. J. Anaesth.*, **32**, 353.

Su, H. H., Kao, F. T., and Karp, M. (1953). The respiratory effect of Ro2-3198 (3-Hydroxy Phenyldimethylethylammonium Bromide) in syncurinized dogs. *Science*, **113**, 743.

Whittaker, V. P. (1951). Idrolisi della succinilcolina da colinesterasi: utilizzazione simultanea della cromatografia su carta e della technica di Warburg. *Experimentia*, **7**, 217.

Zaimis, E. J. (1954). Transmission and block at the motor end-plate and in autonomic ganglia: The interruption of neuro-muscular transmission and some of its problems. *Pharmacol. Rev.*, **6**, 53.

—— (1959). Mechanisms of neuromuscular blockade. *Curare and Curare-like Agents*, by Bovet, D., Bovet-Nitti, F., and Marini-Bettolo, G. B., p. 191. Amsterdam: Elsevier.

U.S.A.: THE LOVELACE CLINIC, situated in the Southwest, is expanding its staff of 52 physicians. As the result of excellent response to previous advertisement further applications for full-time appointments are invited in the field of anesthesiology.

Opportunity for research is available.

Conditions of appointment and detailed information available from:

THE BOARD OF GOVERNORS, LOVELACE CLINIC, ALBUQUERQUE, NEW MEXICO.

Brit. J. Anaesth. (1960), **32**, 372

OBSERVATIONS ON THE EFFECTS OF D-TUBOCURARINE ON THE BLOOD ELECTROLYTES OF THE DOG

BY

D. E. STEVENSON

School of Veterinary Medicine, University of Cambridge, England

THERE are few reports of changes in blood electrolytes due to the use of d-tubocurarine. A decrease in the alkali reserve was reported in dogs by Bracci and Lorenzini (1949) and Lorenzini (1949). Previous papers (Stevenson, 1960a, b) have described the changes which occur during anaesthesia and during suxamethonium relaxation in dogs. The aim of this paper is to assess the changes in blood electrolytes and other events which may arise during the use of d-tubocurarine as a relaxant in dogs.

The methods used in this investigation have already been described (Stevenson, 1959, 1960a, b).

EXPERIMENTAL RESULTS

On the basis of clinical experience in man and a few published veterinary reports (Dinsmore, 1950; Jones, 1950; Brinker, 1950) it was believed that the injection of d-tubocurarine in minimal doses to anaesthetized dogs would produce no serious side effects. The first experiment, however, indicated that in the dog there might be a very real toxicity. The experiment was commenced in the usual manner (Stevenson, 1960a) and when a satisfactory plane of anaesthesia was attained a fairly rapid (within 1 minute) injection of d-tubocurarine (Tubarine) was given at a dose rate of 0.7 mg/kg body weight. After some minutes it was observed that the blood flow through the pH-recording apparatus had ceased. Investigation showed that this was due to low blood pressure. Atropine sulphate (0.65 mg) was given and was followed by neostigmine. Although this partially restored the blood pressure and natural respiratory movements, respiration was insufficient for adequate ventilation even after 4 mg of neostigmine. After about 5 minutes 2 ml of 20 per cent calcium gluconate was given intravenously and almost immediately the depth of respiration improved. Following a further 2 ml calcium gluconate, respiratory movements were capable of maintaining adequate gaseous exchange.

Since it was now known that the serious side effects could be reversed, further experiments were attempted. The first of these is shown in figure 1 by the black circles. Tubocurarine was given this time by a much slower injection, until

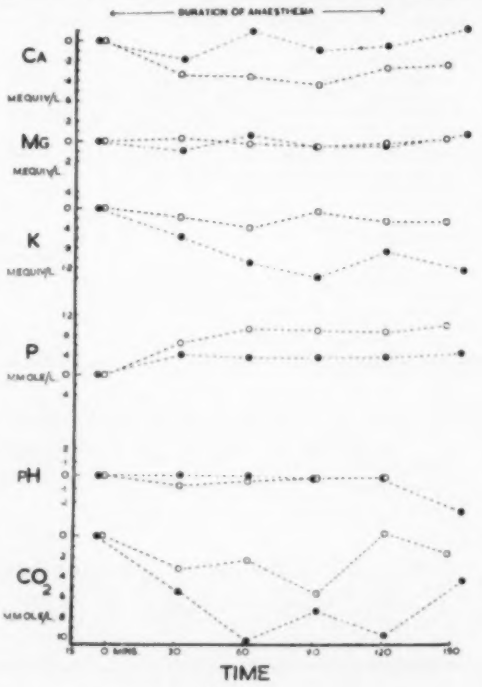


FIG. 1

The variations found from the control concentrations prior to the induction of thiopentone-nitrous oxide anaesthesia in two experiments. Muscle relaxation was obtained by the injection of d-tubocurarine. Spontaneous respiration was restored by the injection of neostigmine after the 120-minute blood samples.

the diaphragm was paralyzed. It was now found that a slow rate of blood flow through the pH-recording apparatus was possible. Examination of the results obtained in this experiment showed that there was a progressive diminution in the arterial content of carbon dioxide and that by 60 minutes this was only about 50 per cent of the control value. It must be remembered that the rate of ventilation was adjusted to keep the blood pH within the normal limits.

It was at first thought that the decreased arterial content of carbon dioxide was due to a fault in the pH-recording apparatus, possibly as a result of the slow rate of flow. Had this been so then hyperventilation would have resulted and the carbon dioxide tension reduced accordingly. However, it was also noted that the plasma inorganic phosphate showed a slight increase. This normally decreases during hyperventilation in the course of anaesthesia in dogs (Stevenson, 1959).

Further experiments, in which d-tubocurarine was given by slow injection over periods of up to 5 minutes, showed that it was possible to achieve relaxation with this agent without inducing a large reduction in the carbon dioxide content of the arterial blood. These results are shown in figure 2.

It may also be seen from the results shown in figures 1 and 2 that in four out of five experiments there was a decrease in the plasma calcium concentration of up to 0.5 m.equiv/1. This was a much greater fall than had been found during anaesthesia alone or during relaxation with suxamethonium (Stevenson, 1960a, b). The magnesium concentration, however, remained constant throughout these experiments.

The changes in potassium concentration were not as consistent as had been found during nitrous oxide anaesthesia alone (Stevenson, 1960a) and in no case was there more than a slight increase after the termination of anaesthesia. Thus it seemed possible that tubocurarine might have an effect on potassium metabolism. There were only slight changes in the plasma inorganic phosphate concentration, but unlike those involving suxamethonium relaxation, these mainly occurred during the first 30 minutes.

The decrease in the carbon dioxide content of blood shown in figure 1 remained of interest. Tubocurarine is known to be a potent liberator of histamine in dogs (Alam et al., 1939). Histamine has long been known to cause a decrease in the alkali reserve (Feldberg and Schilf, 1930). It therefore seemed possible that the release of histamine in the body as a result of the rapid injection of tubocurarine might account for the decrease which had been found in the total carbon dioxide content of arterial blood. It had also been noted during experiments involving the use of tubocurarine that the yield of plasma from a given volume of blood sample gradually decreased from about 50 per cent to as little as 25 per cent, even when the total carbon dioxide content of the blood had not changed. Dale and Laidlaw (1919) observed a similar phenomenon in histamine-induced shock in dogs and cats. They believed that histamine increased the per-

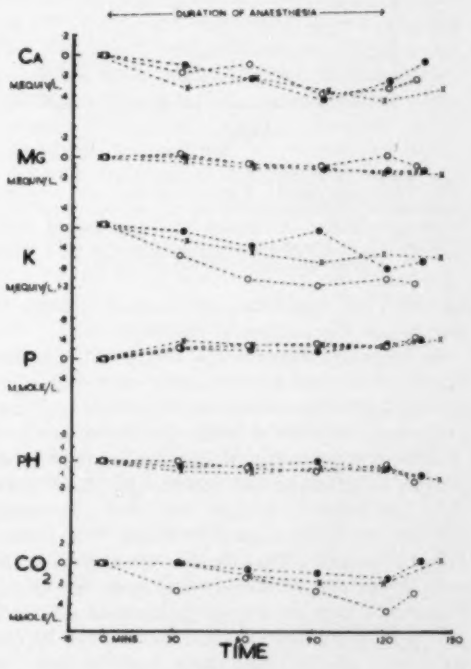


FIG. 2

The results of three experiments in which muscle relaxation was produced by the very slow injection of d-tubocurarine during thiopentone-nitrous oxide anaesthesia.

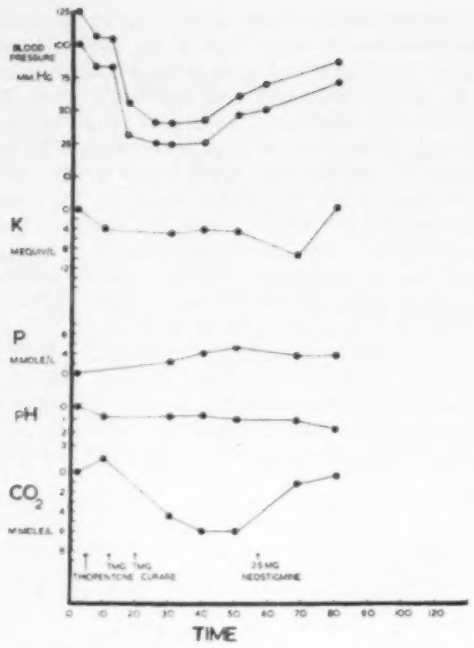


FIG. 3

The effect on blood pressure caused by a rapid injection of d-tubocurarine in an anaesthetized dog weighing 14 kg. A second injection caused little further fall in blood pressure. The time is in minutes from the control blood sample.

meability of capillaries, so allowing plasma to escape into the peripheral tissues.

In order to determine the degree of depression of the blood pressure resulting from the rapid injection of tubocurarine, an experiment was carried out, the results of which are shown in figure 3. This clearly indicated that by the time spontaneous respiration had ceased, the blood pressure had fallen to a very low level. A second injection of tubocurarine produced little further fall at this stage. A progressive diminution in the total blood carbon dioxide was again found and this would have been even greater had the blood pH been maintained at the control level. In this particular case it would have been necessary to deliberately hyperventilate the dog in order to achieve this.

Landmesser (1947) had found that the side effects produced by the injection of curare in dogs, such as bronchoconstriction, could be abolished by the previous administration of antihistaminic drugs. These compounds were not able to prevent completely the fall in blood pressure, however. This was confirmed in experiments in which promethazine was given by intramuscular injection instead of pethidine for premedication. A dose rate of 0.5 mg/kg body weight was used. The experimental procedure was otherwise similar to the experiment shown in figure 3. The results obtained in one of these experiments is shown in figure 4. Although tubocurarine was given by rapid injection, the decrease in the carbon dioxide content of arterial blood no longer occurred, neither was there any evidence of haemoconcentration, as judged by the yield of plasma from blood samples. It was also found that while there was still a fall in arterial blood pressure, this was not as profound or as persis-

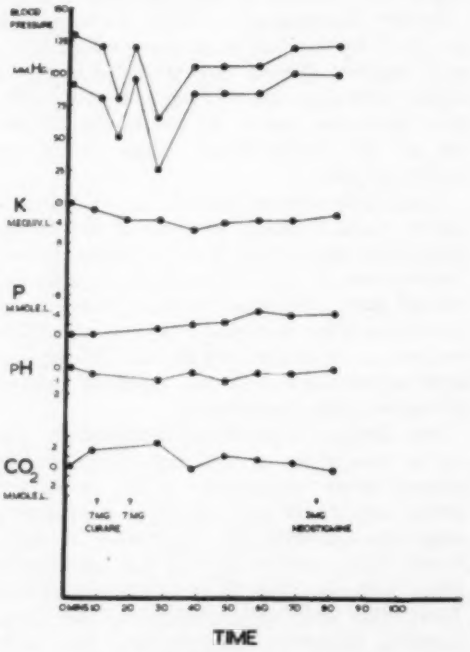


FIG. 4

The effect of d-tubocurarine on the blood pressure of a dog anaesthetized with thiopentone and nitrous oxide following premedication with promethazine 2 mg/kg body weight (15 kg).

tent as was shown in figure 3. It therefore seemed likely that the main metabolic effects of tubocurarine were mediated indirectly through the release of histamine.

In order to confirm that histamine release could cause changes similar to those which had been found after rapid injection of tubocurarine, some experiments were carried out with compound 48/80, a condensation product of p-methoxyphenethyl-methylamine with formaldehyde, which is known to be a specific histamine liberator (Paton, 1951). Figure 5 shows the results obtained in one of these experiments. The control blood sample was taken after the induction of anaesthesia. It will be seen that there was a profound fall in blood pressure and that there was also a progressive fall in the carbon dioxide content of the arterial blood. The potassium concentration showed an increase during the first half of the experiment.

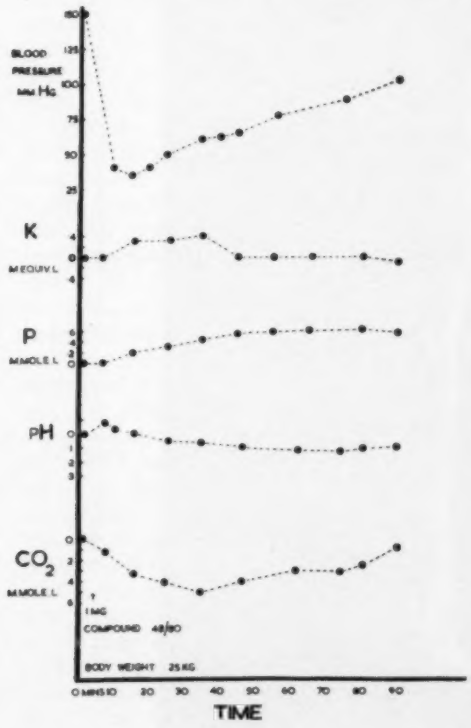


FIG. 5

The effects produced by the injection of compound 48/80 into an anaesthetized dog weighing 25 kg. No artificial respiration was used.

A further observation during the experiments with compound 48/80 was that there was an increase in the pH of arterial blood which persisted for several minutes after the injection of this compound. This increase was of the order of 0.08 to 0.12 pH units and was therefore too great to be explained completely by the decrease in the carbon dioxide content of the blood already noted at this point.

Since calcium had been found to have a beneficial effect after histamine release induced by the rapid injection of tubocurarine, this phenomenon was investigated more fully. It was found that both potassium and calcium ions were capable of elevating the blood pressure of dogs when this had been lowered by the intravenous administration of histamine in a saline drip. This restorative effect was almost abolished by phentolamine but was still present after bilateral adrenalectomy. However, it was found that potassium ions often produced cardiac irregularities or even arrest unless given with calcium.

Figure 6 illustrates an experiment in which the profundity of the fall in blood pressure following rapid injection of tubocurarine needs no comment. The administration of neostigmine had no effect on blood pressure, neither was there any sign of returning respiration 90 seconds later. In some similar experiments a degree of diaphragmatic movement did return at this point but was never sufficient to maintain adequate ventilation. Calcium chloride was then given by intravenous injection and shortly afterwards deep respiratory movements recommenced. At this stage there had been only a slight improvement in blood pressure, so a further injection of calcium was given. This had the effect firstly of increasing the respiratory rate and then the blood pressure, which soon reached the control level. The reversal of the action of curare at the neuromuscular junction was first demonstrated by Feng (1936) and Chao (1936) but the increase in respiratory rate suggests a central rather than a peripheral mode of action in this case.

The intravenous injection of calcium chloride has been found to reverse the hypotension produced by the injection of protamine sulphate in

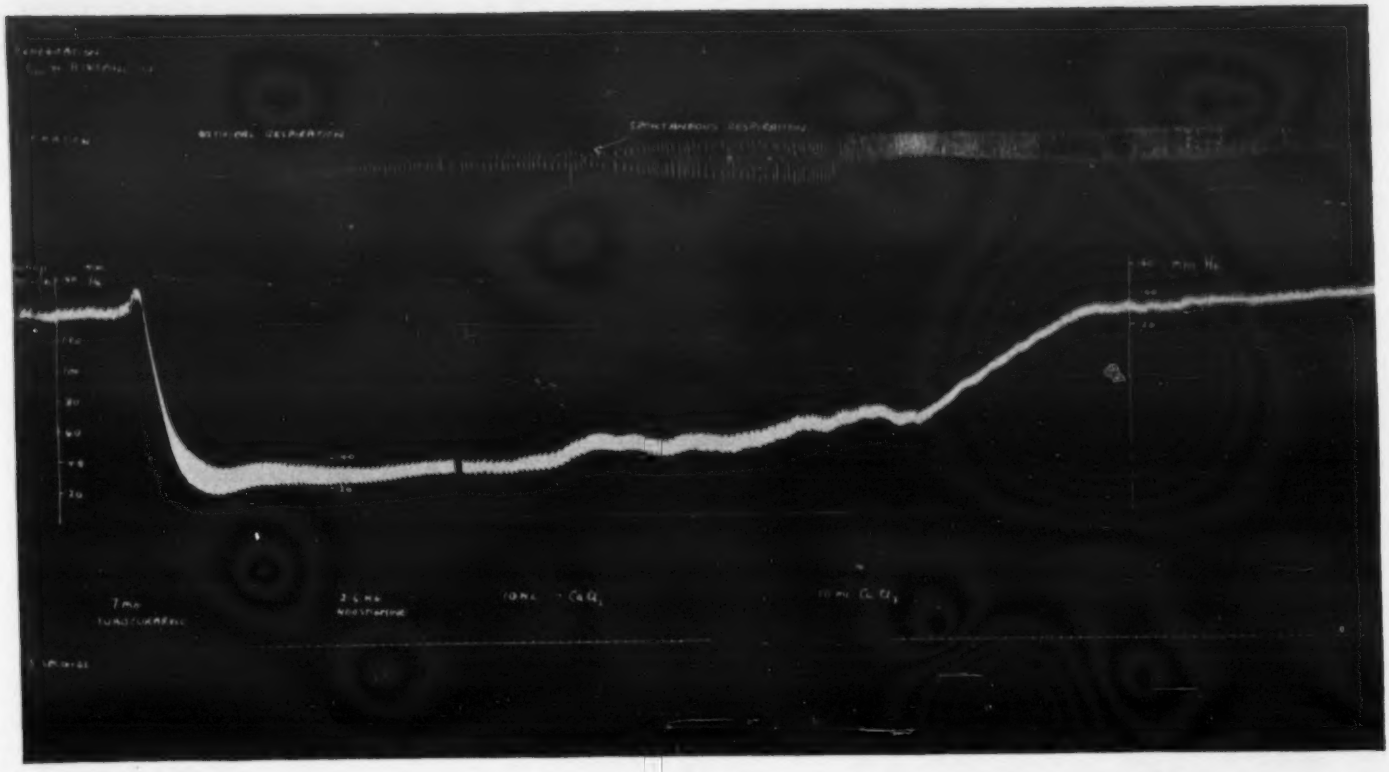


FIG. 6

The effects produced by a rapid injection of d-tubocurarine on the blood pressure and respiration of a 14 kg dog, and the responses obtained by the injection of neostigmine and N calcium chloride.

sensitized dogs and also by the injection of compound 48/80. This effect was first noted by Lio (1927) in histamine-induced hypotension in dogs. It was observed in experiments involving the administration of calcium that unless this was given shortly after the production of hypotension large doses were necessary to induce beneficial changes.

The experiment shown in figure 6 suggested that the respiratory paralysis following the rapid injection of tubocurarine in the dog was due to an action of the drug at a site other than the neuromuscular junction. In order to test this hypothesis, experiments were carried out using dog nerve-muscle preparations. Stimulation of the peripheral end of the divided sciatic nerve was employed to activate the foot flexor muscles in a hind limb (the tibialis anticus and adjacent muscles). The tendon of the gastrocnemius was severed and foot movement was recorded. Figure 7 shows the response obtained in a dog anaesthetized with thiopentone and nitrous oxide. Satisfactory recordings of spontaneous respiratory movements could not be obtained in this experiment, so that only visual observations were made. Prior to the rapid injection of tubocurarine, a tetanic stimulus produced a greater contraction than that obtained from single stimuli. Post-tetanic potentiation of single stimuli may also be seen at this stage. Following the rapid injection of 0.6 mg tubocurarine per kg body weight the blood pressure fell to a very low level and neuromuscular transmission, as judged by respiratory movements and the response to sciatic stimulation, was completely inhibited. Controlled respiration was carried out and two intravenous injections of 2.5 mg neostigmine were given at intervals. This partially restored transmission in the nerve-muscle preparation but there was no evidence of spontaneous respiration at this stage.

There was still no sign of returning diaphragmatic respiration 11 minutes after the initial dose of neostigmine. The administration of calcium at this stage (fig. 8) caused a dramatic increase in blood pressure, at the peak of which diaphragmatic respiration recommenced and within a short time respiration reached an adequate volume. If it is assumed that the diaphragm is more resistant to curarization than the leg muscles, as is found in muscle relaxation obtained by the injection of gallamine in dogs (fig. 9), this experiment suggests that there is a mechanism other than failure of peripheral neuromuscular transmission which is responsible for the lack of response to neostigmine.

It might be argued in the preceding experiments that the effects obtained could be due to the failure of neostigmine to reach the endplate regions at which the drug exerts its effects, due to the profound hypotension. Another type of experiment was therefore designed to test this theory. In this case (fig. 9) muscle relaxation was obtained by the slow intravenous injection of gallamine to a dog anaesthetized with thiopentone and nitrous oxide. Respiration was then controlled for a period of 20 minutes, after which time spontaneous respiration was restored by the administration of atropine followed by neostigmine. An injection of compound 48/80 was given and it can be seen that respiratory movements soon became extremely shallow and less frequent (fig. 10). The recordings at this point were obtained by a tambour connected directly to the endotracheal tube, a procedure which was impossible during controlled ventilation, due to the pressures involved. This respiratory response was completely different from that obtained when compound 48/80 was administered alone, when the depth of respiration was usually decreased while the rate increased, and as a result the animal was able to maintain the pH level of the blood (fig. 5).

DISCUSSION

There are several reports in the veterinary literature concerning the use of curare as a muscle relaxant during anaesthesia in dogs (Dinsmore, 1950; Jones, 1950; Brinker, 1950). In general these have suggested that this agent may produce only minimal side effects and may be considered as a safe muscle relaxant. It is noteworthy, however, that in these reports little attention has been paid to changes in blood pressure. Experimental studies, on the other hand, have shown clearly that curare may have a high toxicity in dogs, for among the symptoms which have been noted following administration are salivation, retching, haemorrhagic diarrhoea, bronchospasm, profound hypotension, haemoconcentration and death (Perlstein and Weinglass, 1945;

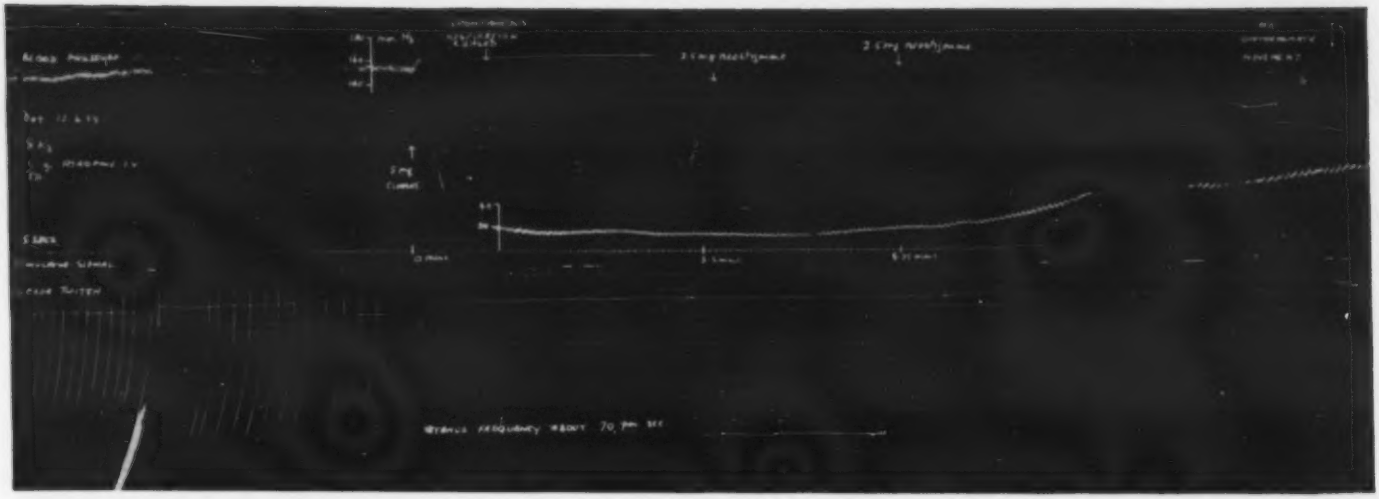


FIG. 7

Dog sciatic nerve-tibialis muscle preparation, showing the responses obtained to the rapid injection of d-tubocurarine and the failure of neostigmine to initiate voluntary respiratory movements.

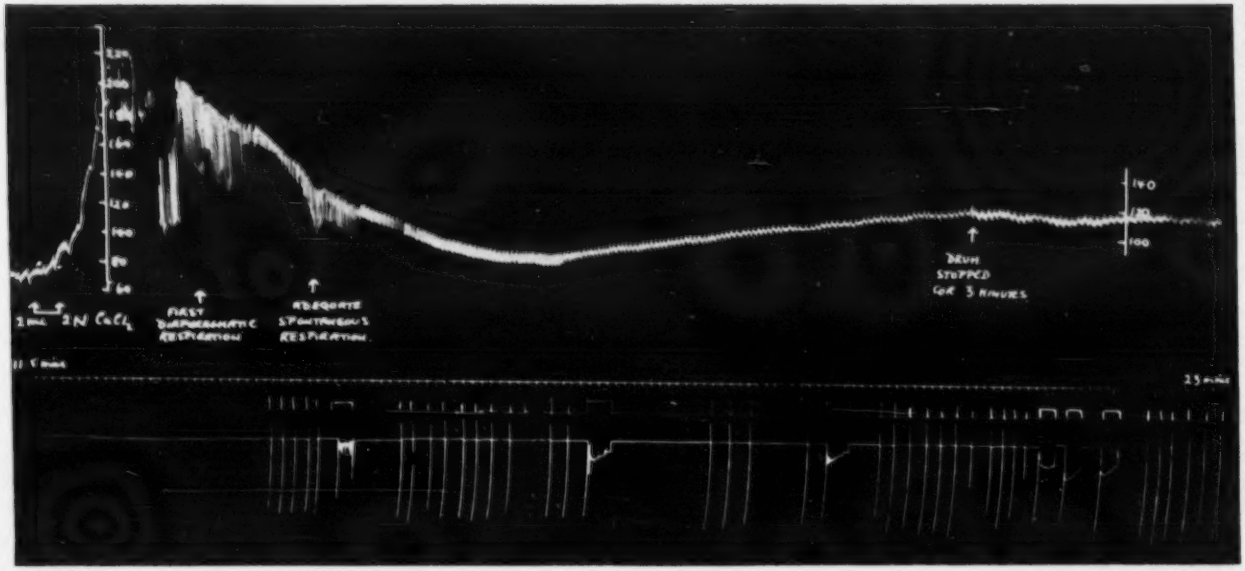


FIG. 8

The same preparation as figure 7, showing the initiation of respiratory movements by the administration of calcium chloride solution. The times marked are from the injection of d-tubocurarine.

Cole, 1946; Cole, Baronofsky and Wangensteen, 1947; Landmesser, 1947; Guyton and Reeder, 1950).

It is now well established that curare may cause histamine release in dogs (Alam et al., 1939; Schild and Gregory, 1947; Reid, 1950) and this may explain most of the side effects which have been noted, although a component of the hypotension may be due to ganglionic blockade (Langley and Dickinson, 1890; Grob, Lilienthal and Harvey, 1947).

In this investigation it has been found that doses of d-tubocurarine which are normally insufficient to cause diaphragmatic paralysis may, if injected rapidly, produce a large decrease in total blood carbon dioxide content. Bracci and Lorenzini (1949) have previously reported a progressive decrease in the alkali reserve of dogs given large amounts of curare. A significant decrease in the total blood carbon dioxide has also been shown in this investigation following the injection of compound 48/80. Paton (1951)

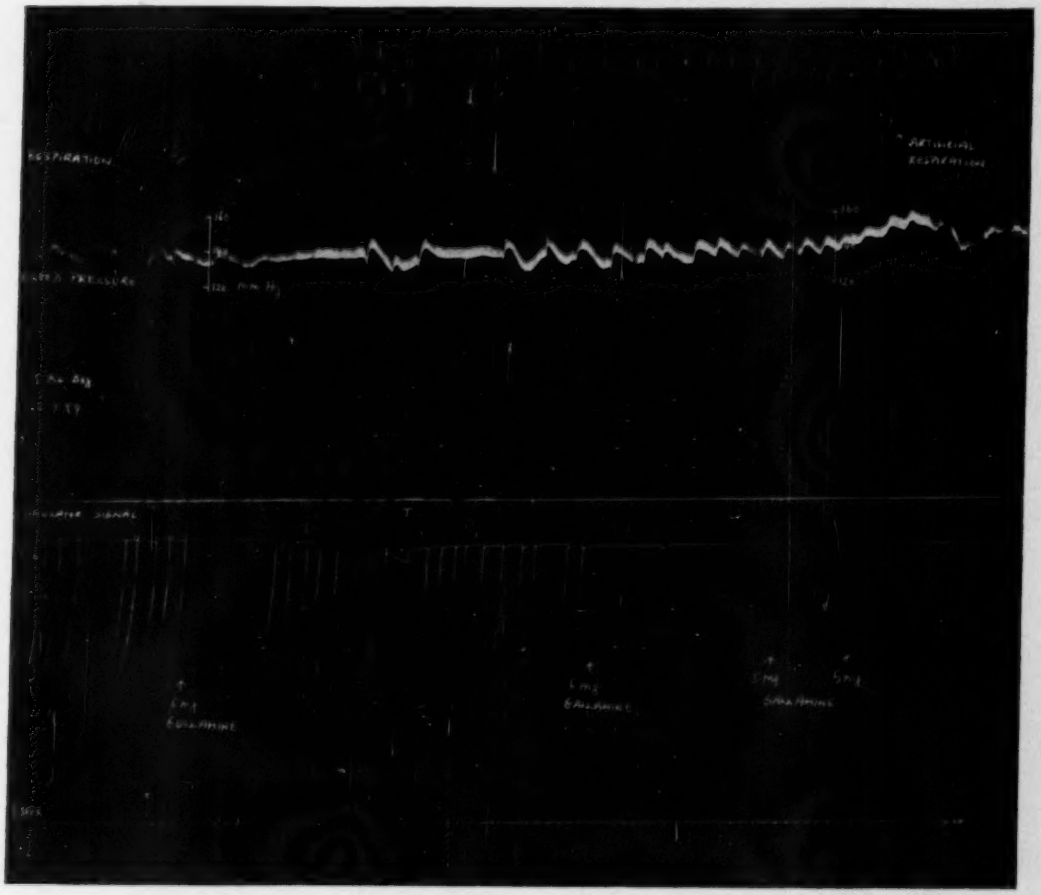


FIG. 9

Dog sciatic nerve-tibialis preparations. The production of neuromuscular block by gallamine, showing that respiration is less sensitive than the twitch preparation to this relaxant.

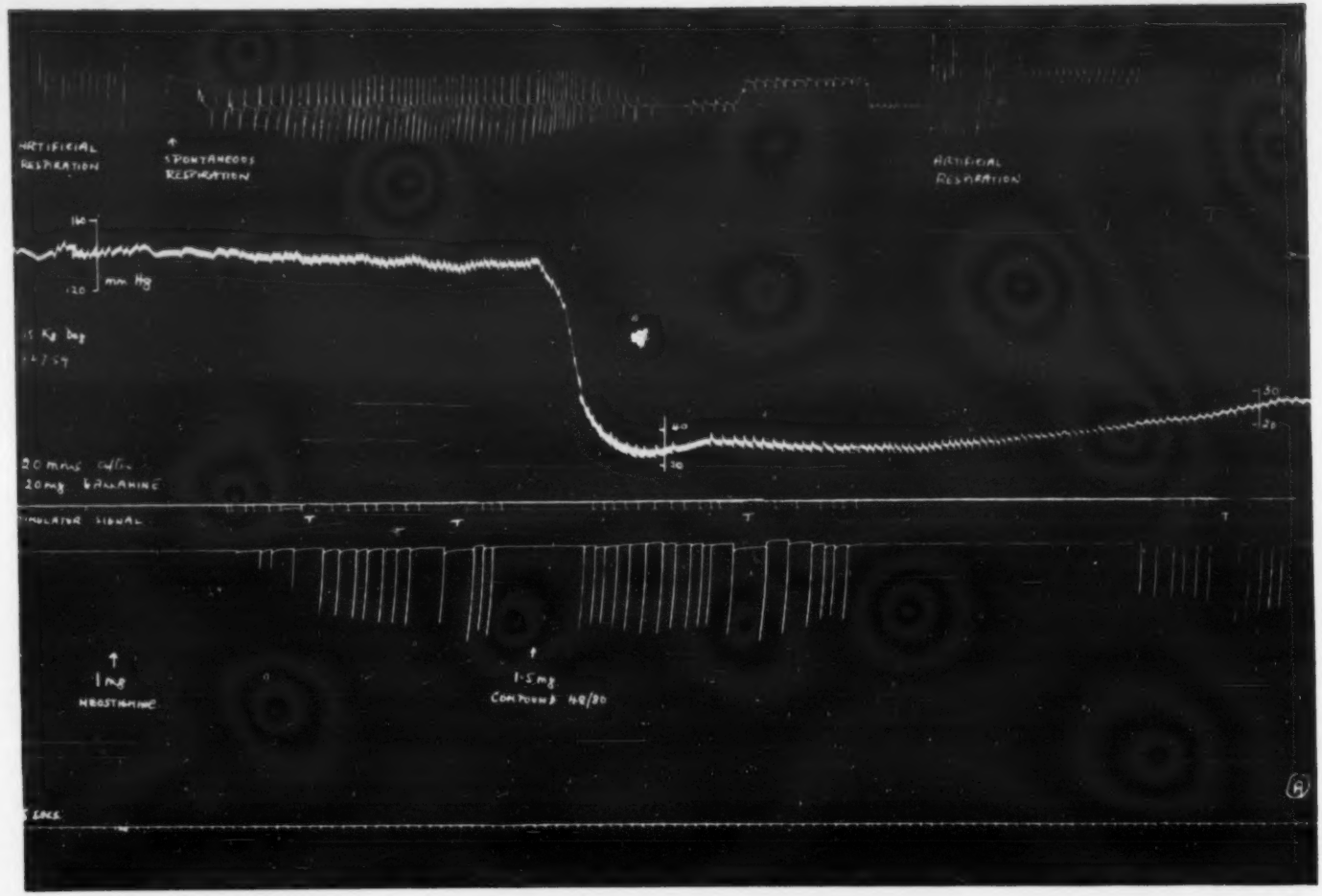


FIG. 10

The same preparation as figure 9, showing the restoration of neuromuscular transmission by neostigmine. Following the injection of compound 48/80, respiration became insufficient to maintain the blood pH, and soon became irregular.

has shown that after the injection of compound 48/80 into dogs the peak plasma concentration of histamine was reached within the first 2 minutes and thereafter rapidly fell away to a low level. The metabolic changes following histamine release therefore appear to be much more lasting than the histamine itself. Paton and Schachter (1951) found that in dogs antihistamine drugs do not prevent the release of histamine caused by the injection of compound 48/80, although these agents stop the appearance of metabolic effects.

It has been noted in this investigation that the administration of both histamine and compound 48/80 appeared to decrease the depth of anaesthesia, since the dogs were often found to start chewing on the endotracheal tube and to have eye reflexes which had been previously absent. It is felt that this is important in view of the statement of Brown and Sellick (1955) that "the signs of too light a level of analgesia are in many cases identical with those of commencing shock," for it is manifestly necessary to distinguish between the two entities before taking therapeutic action.

It must be concluded from these studies that d-tubocurarine is not a safe muscle relaxant for use in dogs, even when the known side effects are prevented by premedication with antihistaminic drugs.

This study has shown that it is possible to produce a condition in dogs during the use of nondepolarizing muscle relaxants in which natural respiratory movements are still absent following the administration of neostigmine by inducing a state of shock by histamine. It seems probable that other methods of producing shock might have a similar effect. This condition may be similar to "neostigmine-resistant curarization" in man. When this study was undertaken it was not known whether a syndrome similar in nature to "irreversible curarization" occurred in veterinary anaesthesia. However, clinical experience in this department has shown that a varying degree of respiratory insufficiency following the use of either type of muscle relaxant may sometimes be encountered in certain types of surgical patient. These are usually cases of acute intestinal obstruction and of acute endometritis (a relatively common serious condition of bitches over 5 years). Death some hours after the termination of surgery has been encountered in some cases where neostigmine had failed to restore adequate respiration and in which adequate artificial ventilation had been maintained and in the period preceding death, the absence of the return of any eye reflexes suggested central depression.

The use of muscle relaxants in severely depressed surgical cases therefore seems a matter for debate. Bairaõ (1959) has advocated the use of curare when surgical intervention is in a reflexogenic area, since the ganglionic blocking properties of this agent may help to protect the patient. On the other hand, Loder (1957) believed that this is not true and has suggested that the use of local analgesics to block the afferent nerves of abdominal organs during surgical intervention resulted in a greatly improved condition of the patient on recovery, even when curare had been used. There is in fact a tendency to adopt a very light plane of anaesthesia in acute abdominal surgery when muscle relaxants are used, since these agents restrain involuntary movements on the part of the patient. As a result the patient may not be fully protected against the effects of manipulation of abdominal organs, a procedure which has often been used to produce experimental shock.

It was first thought that the beneficial effects of the administration of calcium following the induction of hypotension by histamine release might be due to a stimulant action on the adrenal medula (Bacq and Rosenblueth, 1934; Katz and Katz, 1937). However, it was found that this effect was still present after bilateral adrenalectomy (unpublished). The fact that calcium may increase both the rate and depth of respiration in histamine shock, before the blood pressure increased, suggests a complex mechanism of response. It has also been found that the rapidity with which calcium therapy is initiated after the fall in blood pressure induced by tubocurarine, compound 48/80 or protamine has a relationship to the amount needed to produce a beneficial response, since if more than a few minutes had elapsed it was necessary to inject large amounts in order to secure a lasting effect.

In clinical cases of respiratory insufficiency following the use of muscle relaxants, the use

of calcium has been disappointing, since although the depth of respiration is increased there has often been no sign of returning consciousness and the condition of the patient has gradually deteriorated.

When this study was commenced it was believed that extra-cellular electrolytes might play a dominant role in the production of "irreversible curarization" because of the important role these are known to have in neuromuscular transmission. This view has been modified during the course of the investigation and it is now realized that electrolyte changes, whether pre-existing or occurring during anaesthesia, also reflect variations in the energy metabolism of tissue cells. Thus it is necessary to consider both the electrolyte changes themselves, and also the primary events which cause such changes, when forming a hypothesis to explain such events as failure to respond to neostigmine following a period of controlled respiration.

SUMMARY

The rapid injection of clinical doses of d-tubocurarine into anaesthetized dogs produces profound hypotension which is accompanied by a progressive decrease in the arterial carbon dioxide content if the pH is maintained at the preanaesthetic value. These changes may be prevented by the use of antihistamine premedicant drugs.

Following the rapid administration of d-tubocurarine in dogs it may be impossible to restore spontaneous respiratory movements by the injection of neostigmine, although peripheral neuromuscular transmission is restored. The injection of calcium and potassium ions may restore spontaneous respiration if given soon after the induction of hypotension.

Compound 48/80 produces far greater respiratory depression in the presence of gallamine together with neostigmine than when administered alone.

ACKNOWLEDGMENTS

This work was carried out during the tenure of a May & Baker Research Fellowship. The author is grateful to Dr. L. W. Hall, for advice, to Miss B. A. Sheppard for technical assistance, and to Miss J. Minns for help with the preparation of the figures. A supply of compound 48/80 was made available by Dr. A. C. White of Burroughs Wellcome Ltd.

REFERENCES

Alam, M., Anrep, G. V., Barsaum, G. S., Talaat, M., and Wieninger, E. (1939). Liberation of histamine from the skeletal muscle by curare. *J. Physiol.*, **95**, 148.

Bacq, Z. M., and Rosenblueth, A. (1934). The action of calcium and potassium ions on the nictitating membrane, the adrenal medulla and the non-pregnant uterus of the cat. *Amer. J. Physiol.*, **108**, 46.

Bairaõ, G. S. (1959). Present clinical aspects of the use of curare and curariform substances in anaesthesiology. *Curare and Curare-like Agents*, by Bovet, D., Bovet-Nitti, F., and Marini-Bettolo, G. B., p. 435. Amsterdam: Elsevier.

Bracci, U., and Lorenzini, L. E. (1949). Il ricambio organico è modificato dalla somministrazione di curaro in larghe dosi. *G. ital. Anest.*, **15**, 171.

Brinker, W. O. (1950). Use of surital sodium and curare in small animal surgery. *N. Amer. Vet.*, **32**, 832.

Brown, A. I. P., and Sellick, B. A. (1955). Anaesthesia for cardiac surgery. *Brit. med. Bull.*, **11**, 174.

Chao, I. (1936). Action of calcium and curare on muscular contraction and neuromuscular transmission. *Chin. J. Physiol.*, **10**, 545.

Cole, F. (1946). New lethal dose of curare, with some observations on the pathology produced by large doses. *Anesthesiology*, **7**, 190.

—— Baronofsky, I. D., and Wangensteen, O. H. (1947). Curare and shock; the production of hemorrhage into the upper intestine of the dog with large doses of curare. *Surgery*, **21**, 881.

Dale, H. H., and Laidlaw, P. P. (1919). Histamine shock. *J. Physiol.*, **52**, 355.

Dinsmore, J. R. (1950). Curare. *N. Amer. Vet.*, **31**, 395.

Feldberg, W., and Schilf, E. (1930). *Monographien aus dem Gesamtgebiet der Physiologie der Pflanzen und der Tiere. 20: Histamin.* Berlin: Springer.

Feng, T. P. (1936). Studies on the neuromuscular junction. 2: The universal antagonism between calcium and curarizing agencies. *Chin. J. Physiol.*, **10**, 513.

Grob, D., Lilienthal, J. L. jr., and Harvey, A. M. (1947). On certain vascular effects of curare in man. The "Histamine reaction". *Johns Hopk. Hosp. Bull.*, **80**, 299.

Guyton, A. C., and Reeder, R. C. (1950). Quantitative studies on the autonomic actions of curare. *J. Pharmacol.*, **98**, 188.

Jones, L. M. (1950). Some effects of curare upon domestic animals. *N. Amer. Vet.*, **31**, 731.

Katz, G., and Katz, G. (1937). The action of potassium chloride and calcium chloride on the adrenals of the cat. *J. Pharmacol.*, **59**, 284.

Landmesser, C. M. (1947). Study of the bronchoconstrictor and hypotensive actions of curarizing drugs. *Anesthesiology*, **8**, 506.

Langley, J. N., and Dickinson, W. L. (1890). The action of various poisons upon nerve fibres and peripheral nerve cells. *J. Physiol.*, **11**, 509.

Lio, G. (1927). L'azione esercitata dall' istamina sul cuore e sui muscoli in rapporto ad alcuni cationi fisiologici. *Arch. int. Pharmacodyn.*, **33**, 409.

Loder, R. E. (1957). Inadequacy of general anaesthesia for abdominal operations, a possible solution. *Lancet*, **2**, 468.
Lorenzini, L. (1949). Comportamento del cloro ematico e della riserva alcalina nei cani curarizzati. *Boll. Soc. ital. biol. sper.*, **25**, 106.
Paton, W. D. M. (1951). Compound 48/80: a potent histamine liberator. *Brit. J. Pharmacol.*, **6**, 499.
—— Schachter, M. (1951). Influence of antihistaminic drugs on the release of histamine in unanaesthetized dogs. *Brit. J. Pharmacol.*, **6**, 509.
Perlstein, M. A., and Weinglass, A. (1945). Fatal effects of prolonged complete curarization. *Amer. J. Dis. Child.*, **67**, 360.
Reid, G. (1950). Liberation of histamine and heparin by tubocurarine and its circulatory effects in dogs. *Aust. J. exp. Biol. Med. Sci.*, **28**, 465.
Schild, H. O., and Gregory, R. A. (1947). *Proc 17th Int. Physiol. Congress*, p. 288.
Stevenson, D. E. (1959). A study of changes in the blood electrolytes of the dog caused by anaesthesia. Ph.D. Thesis, University of Cambridge.
—— (1960a). Changes caused by anaesthesia in the blood electrolytes of the dog. *Brit. J. Anaesth.*, **32**, 353.
—— (1960b). Changes in the blood electrolytes of anaesthetized dogs caused by suxamethonium. *Brit. J. Anaesth.*, **32**, 364.

BOOK REVIEW

Oxygenotherapy (2nd edition). By L. Binet and M. Bochet. Published by Masson et Cie. Pp. 262; 43 figures. Price 32 N.F.

This work is divided into two parts: (1) Physiological considerations; (2) Oxygen in medical and surgical practice.

After a preliminary note drawing attention to the difference between anoxaemia and hypoxaemia on the one hand and anoxia and hypoxia on the other, the book begins with a description of the results of anoxia, however produced, on the respiratory, cardiac, circulatory and nervous systems and on the changes in the blood and biochemistry of the body and the psychic reactions thereof. This is followed by a chapter on the physiology of respiration and the results that may be expected in animals and man from the inhalation of 100 per cent oxygen. One of these results, and one the importance of which cannot be overemphasized, is the relief of pain. A list of them is given on pages 41 and 42. The use of oxygen in CO poisoning, drowning, electrocution and shock of various origins is fully dealt with. Indeed it would appear from a perusal of this work that there are few ailments to which our flesh is heir that would not be benefited by the early and judicious use of oxygen. The book ends with a long account of the organization of an oxygen service and methods of applying oxygen to the patient.

The authors give us the benefit of a very extensive experience in the use of oxygen and follow it up with a comprehensive bibliography.

E. Falkner Hill

Brit. J. Anaesth. (1960), 32, 384

PREVENTION, DIAGNOSIS AND TREATMENT OF PROLONGED APNOEA

BY

H. C. CHURCHILL-DAVIDSON AND R. P. WISE

St. Thomas's Hospital, London, S.E.1

THE increasing understanding of the mechanism of action of the muscle relaxants has led to a high degree of safety in their use. Nevertheless, the occasional patient is still encountered in whom the response to the drug is greater than anticipated. There are already a number of reports in the literature outlining the almost unlimited number of causes for this prolonged response (Paton, 1958; Churchill-Davidson, 1956, 1959; Foldes, Rendell-Baker and Birch, 1956).

The aim of this review is to analyze the principles for the clinical use of the muscle relaxants with the maximum degree of safety—particularly in the light of recent investigations in neuromuscular transmission.

THE CHOICE OF MUSCLE RELAXANT

Despite numerous attempts to discover new compounds, there are essentially only three drugs in regular clinical use in this country, namely, d-tubocurarine chloride, gallamine triethiodide, and suxamethonium chloride. In earlier days decamethonium iodide enjoyed a spate of popularity, but the absence of an effective antidote, coupled with the possible occurrence of a dual block, has virtually led to its abandonment in most centres.

The choice of a particular relaxant depends largely upon the circumstances of the operation. For example, a short procedure lasting only a few minutes is satisfactorily accomplished with suxamethonium. This drug has certain possible disadvantages—the occurrence of muscle pains in the postoperative period, an excessively prolonged response in the presence of a low plasma cholinesterase concentration, and finally the production of a dual block, which occasionally may occur even after small doses of the drug have been used. Despite these facts, suxamethonium still enjoys widespread popularity which is likely, however, to be lost as soon as an effective short-acting non-depolarizing drug is discovered.

Either d-tubocurarine or gallamine is used for the longer periods of muscle relaxation required in abdominal surgery. The main disadvantage of d-tubocurarine is that it may produce hypotension when used in large doses, although the fall is rarely excessive. In combination with halothane the drop in pressure may be much greater and for this reason gallamine, which has the added advantage in this connection of a raised pulse rate (due to an atropine-like action), is usually employed.

ADMINISTRATION OF RELAXANTS

Theoretically, a test dose of any relaxant is desirable, but the difficulty of assessing the result, coupled with the discomfort to the patient, has prevented its widespread adoption. Nevertheless, the assessment of the dose of relaxant for a particular patient still remains the most important single factor.

Following a period of controlled respiration the initiation of respiratory activity depends upon three factors. These are: firstly, the amount of depression of the respiratory centre caused by the premedication, the use of intravenous analgesics, and the concentration of other anaesthetic drugs in the circulation; secondly, the carbon dioxide level of the blood (the activity of the centre ceases if the level is either too low or too high); thirdly, even when the centre is ripe for activity sometimes a suitable afferent stimulus must be provided to initiate the return of spontaneous respiration—usually this is provided by the surgical stimulus, by movement of the endotracheal tube, or by deflation of its balloon. Bearing these points in mind, muscular relaxation may be obtained either by the use of large doses of a relaxant drug with nitrous oxide and

oxygen analgesia or by smaller doses of relaxant supplemented by a more potent inhalational anaesthetic agent—the duration of effect of such an agent clearly depending upon its speed of elimination from the circulation.

Long-acting intravenous analgesics such as pethidine are difficult to use with controlled respiration because there is no satisfactory method of assessing the effect of a particular dose upon respiratory activity. Such drugs, or a heavy premedication combined with a large induction dose of barbiturate, are often responsible for a delay in the return of respiration at the end of an operation.

The minute volume used with controlled respiration is another important factor, because few anaesthetists are capable of ventilating a patient so accurately that the carbon dioxide tension of the arterial blood remains within the normal range. Underventilation may be very harmful to some patients; mild overventilation should, therefore, always be used, and then one also knows on which side of the fence one lies. At the end of operation the patient should not be left for periods of apnoea in order to allow the carbon dioxide level of the blood to rise; this practice merely causes periods of asphyxia. Rather, it is better to turn off the carbon dioxide absorber and then ventilate the lungs with a high flow of gases (such as 14 litres per min, which approximates to twice the normal resting minute volume) to which 5 per cent carbon dioxide has been added.

If the carbon dioxide tension of the arterial blood (P_{CO_2}) is low, due to mild overventilation during the operation, it will rapidly rise towards the normal physiological level. On the other hand, if the anaesthetist has unwittingly allowed the carbon dioxide level to rise then the high flow of gases with overventilation will minimize any further rise. Assuming normal respiration is not resumed within 5 minutes then the concentration of carbon dioxide should be reduced to 2 per cent and the mild overventilation continued. Theoretically, in these circumstances the P_{CO_2} level of the blood should gradually approach normality whether the previous level be high or low. Such a method is designed for guidance in clinical practice where accurate instrumentation is not available. It tends to prevent violent fluctuations in the carbon dioxide level of the blood, thus producing conditions suitable for the return of normal respiration and at the same time neither anoxia nor carbon dioxide accumulation can occur.

The use of anticholinesterase drugs to reverse any residual effects of the muscle relaxants is also important. It is often suggested that such drugs should not be used in the presence of apnoea and should only be given once the first signs of respiration have occurred. This caution is unjustified. Following even a small dose of a muscle relaxant neuromuscular transmission does not appear to return to normal for at least 1 to 2 hours. Ninety per cent recovery is usually achieved rapidly but the attainment of complete normality is a long process in the anaesthetized patient. The administration, therefore, of 2.5 mg neostigmine methylsulphate (preceded by 1 mg atropine sulphate) in such cases is always followed by some improvement in neuromuscular transmission.

DIAGNOSIS OF APNOEA AND RESPIRATORY INADEQUACY

The term "prolonged apnoea" has never been satisfactorily defined but a patient should certainly be breathing satisfactorily within 10 minutes of the end of operation. Alternatively, respiratory activity may start but the minute volume be inadequate. In either case the correct diagnosis of the underlying cause is essential. Briefly there are three main causes—those due to depression of the respiratory centre, those due to mechanical defects in the respiratory system and those due to peripheral causes which can usually be directly related to the use of a muscle relaxant.

The only satisfactory method of distinguishing a peripheral cause from the other two groups is by the use of a peripheral nerve stimulator (fig. 1). It is known that the respiratory muscles of normal patients always recover their activity before the hand muscles. Therefore, if on peripheral nerve stimulation there is marked activity of the muscles in the hand it can safely be concluded that the respiratory muscles have also recovered from the effects of the muscle relaxant and consequently the cause of the apnoea must

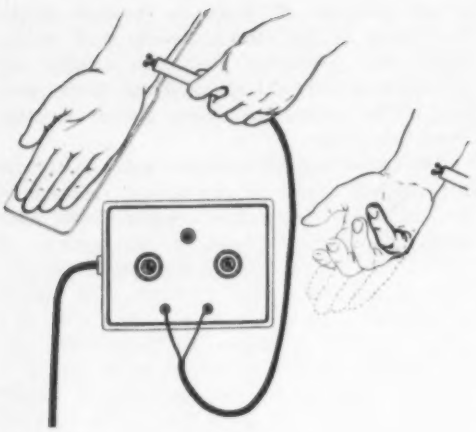


FIG. 1

be of central or mechanical origin. The only exception to this rule is found in certain severe cases of myasthenia gravis where the respiratory muscles rather than the upper limb muscles are principally involved in the disease. These cases can always be detected by an adequate clinical history and examination before operation. On the other hand, if the nerve stimulator produces only a very weak or absent response in the hand muscles, a prolonged action of the relaxant must be suspect. Frequent use of a nerve stimulator soon enables the anaesthetist to detect even minor degrees of paresis. Furthermore, it is also possible to diagnose the exact type of neuromuscular block present at a particular moment. This is particularly useful when dual block is suspected but is also of value in assessing the effectiveness of the reversal of a d-tubocurarine block by an anticholinesterase drug. The electrical changes that occur with both a depolarization and a nondepolarization block have already been described (Churchill-Davidson and Christie, 1959). The mechanical movements of the hand and finger muscles are just as characteristic—thus:

Depolarization block.

The responses are similar whether fast (tetanic) or slow (twitch) rates are used (fig. 2), and there is no improvement in the response after a prolonged burst of tetanus, and no post-tetanic facilitation.

Nondepolarization block.

A fade is seen in both the mechanical and the electrical response to fast and slow rates of stimulation (fig. 3). Furthermore, following a prolonged burst of tetanus there is a temporary but marked improvement in neuromuscular transmission, indicating post-tetanic facilitation. This type of response is diagnostic of a nondepolarization block and it can be confidently anticipated that a suitable dose of an anticholinesterase drug will remove the "fade" in the responses and lead

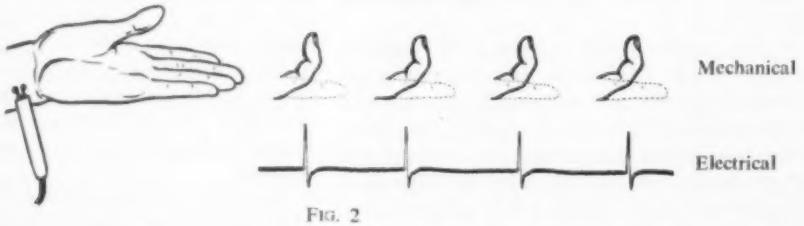


FIG. 2

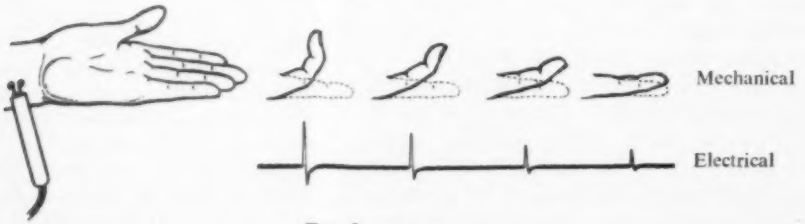


FIG. 3

to an improvement in neuromuscular transmission. If this response is found after the use of a depolarizing drug then a dual type of neuromuscular block is present.

Confronted with the problem of the patient who fails to breathe adequately at the end of an operation some suggestion of the cause may be given by the rate and nature of the respiratory movements. A slow rate suggests central respiratory depression, whereas a more rapid rate together with the use of the abdominal and accessory muscles of respiration (and tracheal tug) points to either a mechanical fault or a peripheral cause due to the muscle relaxant.

The use of the nerve stimulator will rapidly differentiate between a central and a peripheral cause. A mechanical cause of inadequate ventilation, however, is more difficult to diagnose and is sometimes overlooked. In a patient who has just undergone an abdominal operation the use of a stethoscope alone on the thorax often does little more than suggest "bronchospasm". Contrary to time-honoured belief it is possible to demonstrate postoperative pulmonary collapse radiologically within minutes of the end of an operation. Similarly, a pneumothorax due to a ruptured bullus may be the cause of the mechanical defect, or alternatively simple bronchospasm may be present. This latter diagnosis (because it is so simple) should never be made until all other causes of a mechanical defect have been excluded. If a mechanical defect of the respiratory system is suspected then it is essential that an X-ray picture is taken immediately.

TREATMENT

It is important to emphasize that there is no direct evidence to suggest that the muscle relaxants are ever responsible for a fatal outcome. On the contrary, provided adequate ventilation is maintained, there is abundant evidence that massive doses of these drugs can be used for a week or more without ill effect. The most essential element of treatment, therefore, is to ensure that both the oxygen and carbon dioxide tensions of the patient's blood are kept normal. In a patient with severe emphysema the preoperative level of carbon dioxide in the blood may be high and great difficulty may be experienced in restarting respiration unless the relevant laboratory data are available.

The emphysematous patient who comes to operation with a high blood P_{CO_2} may prove particularly difficult to manage postoperatively. Without adequate laboratory facilities it is extremely difficult for the clinician to judge when the carbon dioxide tension of the blood has reached the pre-operative figure. In anaesthesia there is no satisfactory substitute for accurate measurement and it seems certain that in the future most hospitals will need to be equipped with suitable apparatus for this type of case.

The administration of an analgesic-antagonist (where indicated) or a central nervous system stimulant (such as nikethamide) in order to increase the sensitivity of the respiratory centre may help to restart the breathing.

If a peripheral cause is responsible for the apnoea the line of treatment depends upon the diagnosis of the type of neuromuscular block that is present. If a depolarization block is found by the stimulator, then only measures designed to improve the cardiac output, the peripheral circulation and the renal excretion will prove helpful. An abundant supply of patience is the most essential factor in the treatment. On the other hand, if a nondepolarizing type of block is present, then an adequate dose of anticholinesterase drug should be given. A maximum dose of 5 mg of neostigmine should not be exceeded except in those patients in whom the initial dose yields positive evidence of some improvement in neuromuscular transmission and yet a "fade" of the mechanical response still persists.

ACKNOWLEDGMENTS

We wish to thank Dr. M. D. Nosworthy for his help in the preparation of this paper, Miss Joan Dewe for the illustrations—which were photographed by Mr. T. W. Brandon—and Miss Jean Davenport for secretarial assistance.

REFERENCES

Churchill-Davidson, H. C. (1956). Neuromuscular block in man. *Anesthesiology*, **17**, 88.

—— (1959). Causes and treatment of prolonged apnoea. *Anesthesiology*, **20**, 535.

—— Christie, T. H. (1959). The diagnosis of neuromuscular block in man. *Brit. J. Anaesth.*, **31**, 290.

Foldes, F. F., Rendell-Baker, L., and Birch, J. H. (1956). Causes and prevention of prolonged apnoea with succinylcholine. *Anesthesiology*, **35**, 609.

Paton, J. W. (1958). Possible causes of prolonged apnoea. *Anaesthesia*, **13**, 253.

Brit. J. Anaesth. (1960), **32**, 388

THE USE OF THE GOLDMAN HALOTHANE VAPORIZER IN THE CLOSED CIRCUIT

BY

F. R. GUSTERSON AND J. M. CLARK

Worthing Group Hospitals

MANY anaesthetists still hesitate to use halothane in the closed circuit in spite of increasing evidence as to the clinical safety and economy of this method. Marrett (1957) gives a very careful and accurate description of a closed circuit method. He has also shown that there is no build-up of concentration in the fully closed circuit as used by him (Marrett, 1959). Newman (1958) has also claimed that from a theoretical point of view there will be no build-up in the closed circuit provided the halothane vaporizer is not fully efficient.

Recently Duncan and Raventós (1959) have produced evidence supporting this absence of build-up and showing that halothane is rapidly absorbed into the body fat. They calculated that, under ordinary conditions, 20 hours of anaesthesia would be necessary in order to reach saturation of the body's fat deposits.

The problem has been to find a suitable simple vaporizer for halothane in the closed circuit. Marrett's apparatus is excellent, but is not in common use. In this group of hospitals the Rowbotham trichloroethylene vaporizer (Burton, 1958) was used originally but, while this was satisfactory, difficulties arose because different makes of vaporizer gave appreciably different concentrations of halothane.

The use of halothane in the ether vaporizer of a Coxeter-Mushin or Circle Absorber is not satisfactory. Evidence is given below to show the dangers of this method. Initially produced for dental use (Goldman, 1959), the Goldman halothane vaporizer seemed suitable for use in the semiclosed and fully closed circuits in general surgery. This report is based on the measurements of the halothane concentrations obtained by the use of this vaporizer in a series of over 1,000 patients anaesthetized during a period of one year. Full records have been kept of 35 cases and many other readings were taken. Figure 1 shows the position of the vaporizer in the circuit.

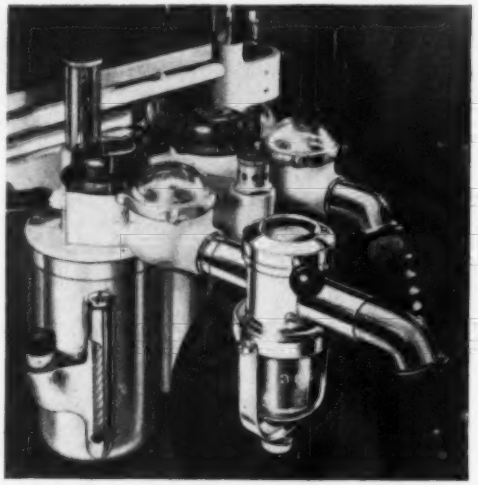


FIG. 1
Goldman vaporizer in position on Circle Absorber.

In all patients anaesthesia was induced with thiopentone followed by a small dose of suxamethonium. A cuffed endotracheal tube was then passed and recordings were commenced after spontaneous respiration was fully established. All recordings were made during routine operating lists. The percentage of halothane was measured by means of a rapid infra-red gas analyzer.* This was calibrated before and after each case, using a known mixture of halothane in nitrous oxide 50 per cent, oxygen 50 per cent.

* Supplied by Infra-red Development Co., Welwyn Garden City.

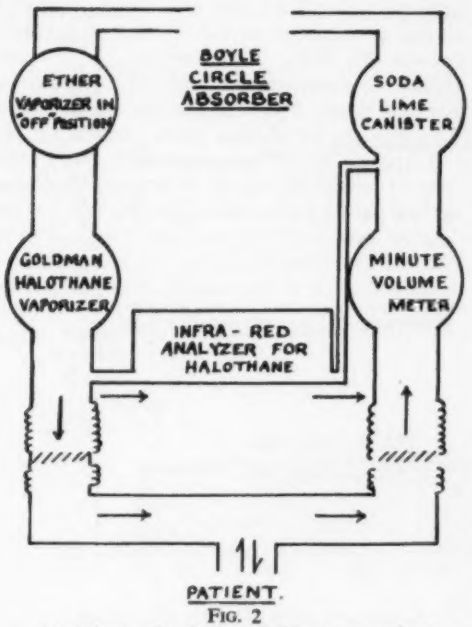


FIG. 2
Anaesthetic circuit for Goldman vaporizer.

The diagram (fig. 2) shows the layout of the circuit and the points at which the gases were sampled and returned. The gas mixture was sampled from a point near the halothane vaporizer on the inspiratory side and the gas, after analysis, was returned to the circuit after the patient's expirations had passed through the volume meter. All pulse and blood pressure readings were taken with a pulse recorder of Bishop's (Bishop, 1958) pattern slightly modified by one of us (J.M.C.). Minute volumes of respiration were recorded using a Dräger Volumeter.

Figure 3 shows the halothane concentrations which were obtained using the method of Brown and Woods (1958) in which the halothane is placed in the ether vaporizer of the Coxeter-Mushin absorber unit. The graph shows extremely well the sudden increases of halothane concentration obtained on altering the drum settings. These concentrations are much too high for safe use, even though they may occur for only short periods of time.

Figures 4 and 5 were obtained with a standard Goldman vaporizer into which a thermometer

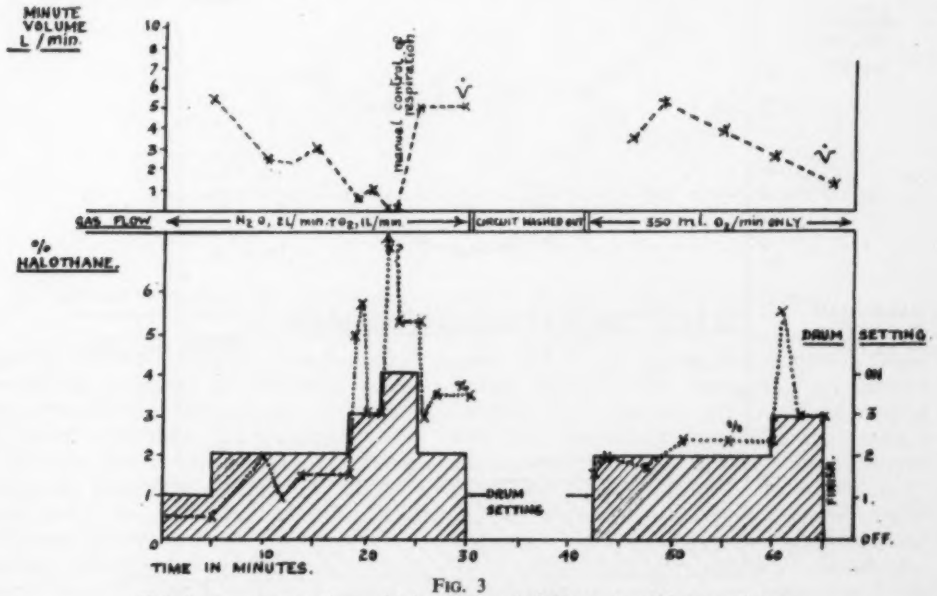


FIG. 3
Halothane concentrations obtained using halothane in ether vaporizer. Coxeter-Mushin absorber. Menisectomy.

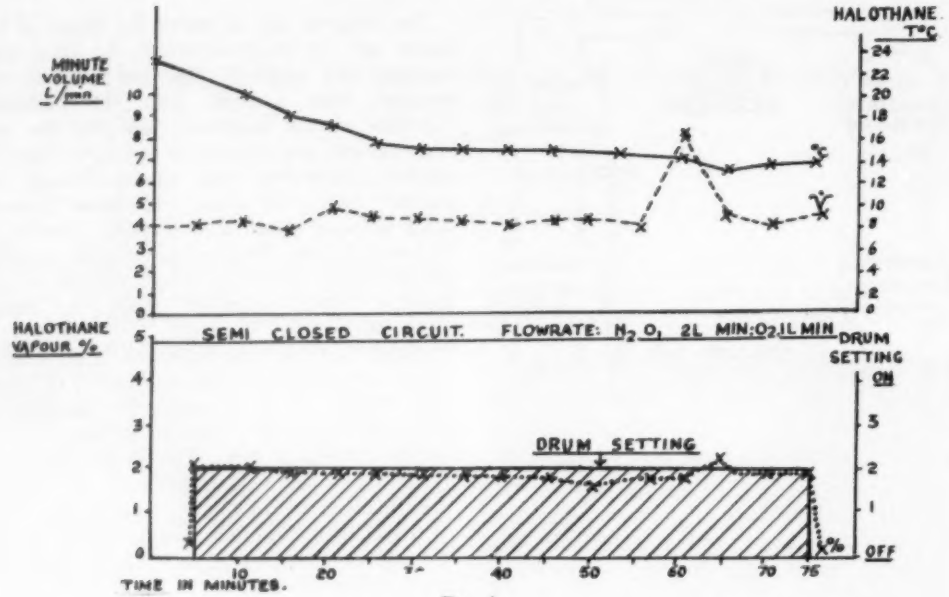


FIG. 4
Halothane concentrations using Goldman vaporizer. Semiclosed circuit. Perineal floor repair.

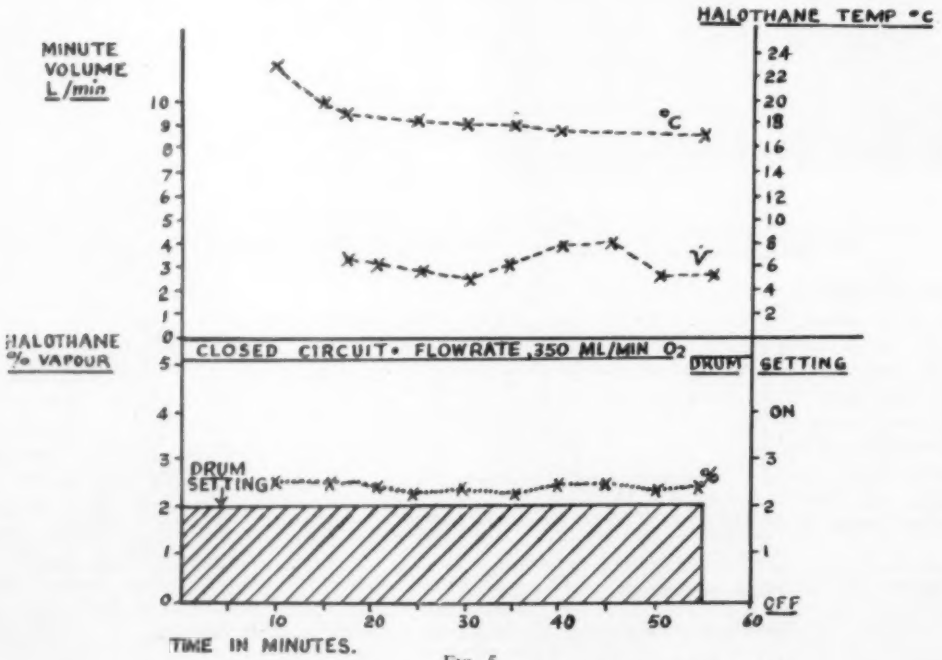


FIG. 5
Halothane concentrations using Goldman vaporizer. Fully closed circuit. Perineal floor repair.

had been fused into the halothane container. They show that a fall in temperature occurs which is less marked after about 40 minutes anaesthesia. This fall in temperature is slightly greater in the semiclosed circuit, which accounts for the rather lower concentrations compared with those obtained in the closed circuit. The remarkable constancy of the halothane concentration over the whole anaesthetic period will be noted in both these figures. The sudden increase in minute volume shown between 55 and 65 minutes in figure 4 occurred at the commencement of the posterior repair during a colporrhaphy.

The analyzer was of the continuous recording type.

Figure 7 compares the different concentrations obtained with the vaporizer in semiclosed and fully closed circuits in the same patient. The slightly higher concentrations in the fully closed circuit are due to the difference in rate of cooling as explained above, and not to tissue build-up. Even after 60 minutes, the return to the same lower concentration when the drum setting was reduced from "2" to "1" demonstrates the absence of tissue saturation over this period.

The mean halothane concentrations obtained for each drum setting in semiclosed and fully

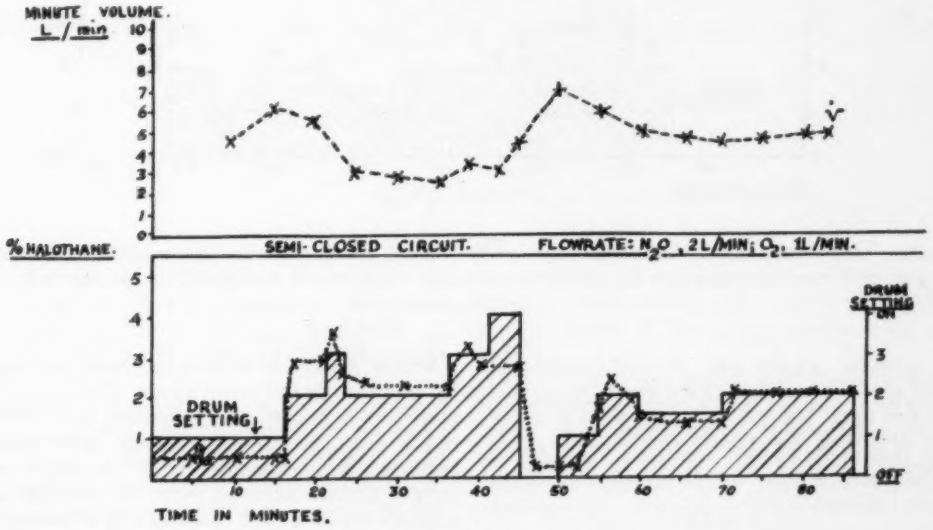


FIG. 6

Halothane concentrations using Goldman vaporizer. Semiclosed circuit. Hemicolectomy.

Figure 6 shows the complete record during a hemicolectomy. It shows the halothane concentrations obtained with different drum settings of the Goldman vaporizer in the semiclosed circuit with an input gas flow of 3 litres per minute, and also the immediate response of halothane concentration to the different drum settings even after 60 minutes anaesthesia.

Readings were taken at 5-minute intervals or whenever the vaporizer setting was changed. closed circuits are summarized in table I. These figures represent the averages of the results obtained in 35 patients, and it will be evident from the previous diagrams that the patient's minute volume is a factor which influences the actual concentration obtained.

These cases shown are typical of all the recordings and it has now become our practice to use the Goldman halothane vaporizer routinely for the administration of halothane. Johnstone (1959)

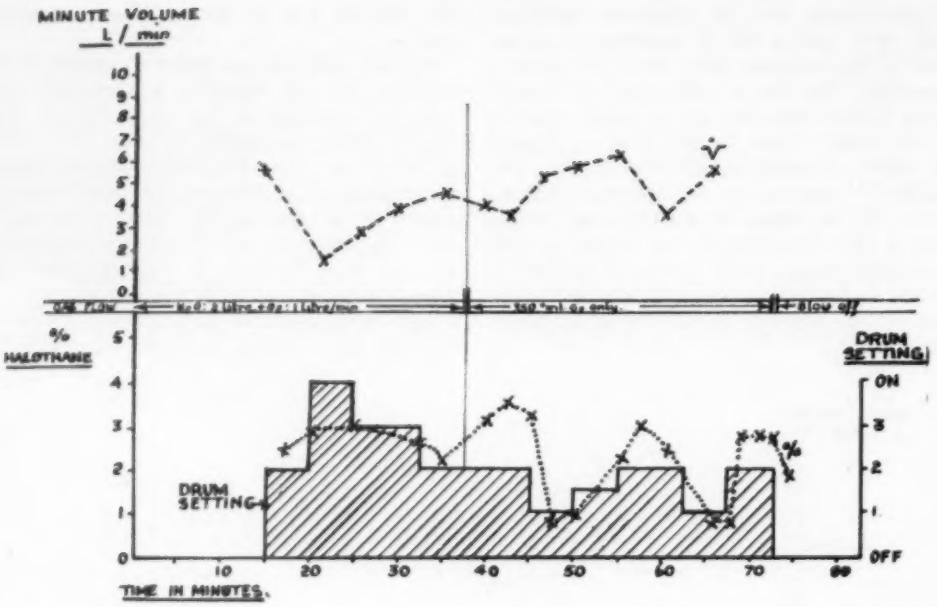


FIG. 7

Halothane concentrations using Goldman vaporizer. Fully closed and semiclosed circuit. Prostatectomy.

has recently pointed out the undesirability of using nitrous oxide in a closed circuit with small gas flow rates. The use of oxygen alone at a flow rate of 1 litre per minute obviates this disadvantage.

TABLE I

Halothane concentrations obtained with Goldman vaporizer in closed and semiclosed circuits.

Drum position	3 litre/min gas flow. Semiclosed circuit. % Halothane	350 ml O_2 basic flow. Closed circuit. % Halothane
1	0.5	1.0
2	2.0	2.5
3	3.5	3.5–4.5
ON	2.8	4.5

Finally, it must be stressed that with halothane the ultimate control must be the clinical assessment of the patient, and a constant and careful watch must always be kept on the pulse, blood pressure and respiration. The possibility of carbon dioxide retention with the low minute volumes obtained with halothane is obviously a matter which requires investigation. Work has already been started on this subject, which will be published when complete.

SUMMARY

The use of the Goldman halothane vaporizer in the semiclosed and fully closed circuit is described and evidence is given of the concentrations of halothane inhaled by the patient using this method. Evidence is provided showing there is no build-up of halothane concentration during the period of any normal operation. The method is economical and simple.

ACKNOWLEDGMENT

We are indebted to Dr. Bracken of British Oxygen Research and Development Co. Ltd., who supplied the thermometer-mounted vaporizer, and for his help in the preparation of the graphs.

REFERENCES

Bishop, C. (1958). A combined pulse indicator and sphygmomanometer. *Anaesthesia*, **31**, 329.

Brown, T. A., and Woods, M. A. (1958). Halothane in a country hospital. *Brit. J. Anaesth.*, **30**, 333.

Burton, P. J. C. (1958). Halothane concentrations from a Rowbotham's bottle in a circle absorber. *Brit. J. Anaesth.*, **30**, 312.

Duncan, W. A. M., and Raventós, J. (1959). The pharmacokinetics of halothane anaesthesia. *Brit. J. Anaesth.*, **31**, 302.

Goldman, V. (1959). Fluothane in the dental surgery. *Cur. Res. Anaesth.*, **38**, 192.

Johnstone, M. (1959). Collapse after halothane. *Anaesthesia*, **14**, 410.

Marrett, H. R. (1957). Halothane: its use in the closed circuit. *Brit. med. J.*, **2**, 231.

—— (1959). Halothane: its use in the closed circuit. *Anaesthesia*, **14**, 28.

Newman, H. G. (1958). Halothane and rebreathing. *Brit. J. Anaesth.*, **30**, 555.

BOOK REVIEW

Cardiac Resuscitation. Edited by J. Willis Hurst, Professor and Chairman, Department of Medicine, Emory University School of Medicine, U.S.A. Published by Charles C. Thomas, Illinois (1960). Pp. 141; illustrated.

This book is a report of a Symposium designed and organized by the Department of Medicine of Emory University School of Medicine held on October 3, 1958, at the Grady Memorial Hospital, Atlanta, Georgia. This is a very full description of the various aspects of cardiac resuscitation but a considerable part of it deals with this problem from the point of view of the physician rather than the surgeon or anaesthetist. The techniques of cardiac massage and of respiratory resuscitation, particularly by direct mouth-to-mouth breathing, are well covered and illustrated. There is a variation in style of writing between the several contributions and some of it is not acceptable to the English reader, as for example "man is recognized as a human being, distinctly different from other life forms, by the total expression of his various organs acting as a unit".

The reviewer was particularly pleased to find the following paragraph in the first chapter: "After one masters the techniques of cardiac massage and pulmonary resuscitation and has thought through his actions prior to facing that emergency he will realize another problem. Who should be resuscitated? In many instances the indications for 'cardiac resuscitation' are clear-cut. In other situations cardiac resuscitation is clearly not indicated. In still other situations one must state that the desirability of action or inaction is uncertain."

In summary this book was most enjoyable to read, is comprehensive and can be recommended.

Cecil Gray

BOOK REVIEWS

Surgical Aspects of Medicine. Edited by H. Daintree Johnson. Published by Butterworth & Co. Ltd., London, 1959. Pp. 382; illustrated. Price 65*s*.

This book has been written to guide the busy physician and family doctor in deciding when to seek surgical aid for their patients. Forty eminent authors have written forty-two chapters covering not only the most common problems which the editor considered involved difficult decisions, but also recent progress in less frequented fields. By discussing briefly the choice of surgical procedure with information on present day mortality and morbidity, side effects and late complications, this book is most valuable to the anaesthetist who aids and abets the surgical correction of disease. The sections giving advice on the management of the patient's life subsequent to operation are most informative.

Direct comments on anaesthesia are few but complimentary. In the chapter on hernia it is noted that "contraindications to operation have been much reduced by thorough preoperative care and by skill of the modern anaesthetist. Age, in itself, is no bar. Many patients over the age of 90 years have been successfully operated on." Comment is made on the influence of poor relaxation on the table resulting in tearing of sutures leading to incisional hernias. In the chapter on "Infective Lung Conditions" it is stated that "no general anaesthetic for an elective surgical procedure should ever be given in the presence of dental sepsis. It is the responsibility of the surgeon to recommend this treatment and of the anaesthetist to see that it has been carried out." This is an excellent example of the sound commonsense, practical information to be found in this book.

The reviewer particularly enjoyed the sections on the clinical management of haemorrhage associated with peptic ulcer, the lucid discussions on portal hypertension and hypersplenism, heart diseases and backache. The section on prostatic enlargement reviews the various surgical manœuvres without bias. Those with sons are recommended to peruse the learned and fascinating chapter on circumcision and those with no heirs the chapter on infertility. Most chapters have a useful bibliography for further reading. Though not primarily designed for anaesthetists this is a book well worth reading both for interest and all round practical information. It is recommended to all anaesthetists and not only to those preparing for the surgical part of the final examination.

I. C. Geddes

Xylocaine—the Pharmacological Basis of its Clinical Use. By Sten Wiedling. Published by Almqvist & Wiksell, Stockholm, 1959. Pp. 146; illustrated.

This comprehensive monograph surveys the now extensive and widely scattered literature on the pharmacology of lignocaine (Xylocaine). Dr. Wiedling draws together over 330 references not only on its local anaesthetic activity but also the effects of lignocaine on virtually all the organs of the body. The data is clearly presented with the use of nine tables and twenty-four figures, thus making this monograph especially valuable to investigators seeking a local anaesthetic superior to lignocaine. Authors wishing to support clinical papers with pharmacological data of local anaesthetics would be advised to study this monograph closely. A full bibliography and both author and subject indexes are appended.

I. C. Geddes

Printed in Great Britain by John Sherratt & Son, Park Road, Altrincham

trophenium

REGD.

phenactropinium chloride

an agent for the production of controlled hypotension during general anaesthesia, providing ganglion blockade without direct vasodilator action. This original product of the Duncan Flockhart Research Laboratories is now available in the new, more convenient, pack of 20 ml. (1,000 mg.) in a box of 6 injection-type vials.

References: "The use of a homatropinium derivative to produce controlled hypotension" *Brit. J. Anaesth.* **29**, 342.

"Comparison of two hypotensive agents" *Anaesthesia*, **14**, 53.

"The use of Fluothane and Trophenium in anaesthesia for the surgery of deafness" *Scot. med. J.*, **3**, 496.

DUNCAN FLOCKHART OF EDINBURGH

The Doctors' House

Duncan, Flockhart & Co. Ltd., Edinburgh 11. aar 274m

BRITISH JOURNAL OF ANAESTHESIA

VOLUME XXXII, No. 8 *Published monthly* AUGUST 1960

Annual subscription (post free): Inland £3 15s.; Overseas £4 4s.: U.S. and South Americas $12.00

CONTENTS

PAGE

EDITORIAL 345

ORIGINAL

The Solubility of Volatile Anaesthetics in Oil 346

By J. F. Nunn, Ph.D., M.B., Ch.B., F.F.A.R.C.S., Research Department of Anaesthetics, Royal College of Surgeons of England, Lincoln's Inn Fields, London, England.

1. Changes caused by Anaesthesia in the Blood Electrolytes of the Dog 353
2. Changes in the Blood Electrolytes of Anaesthetized Dogs caused by Suxamethonium 364
3. Observations of the Effects of d-Tubocurarine on the Blood Electrolytes of the Dog... 372

By D. E. Stevenson, M.A., Ph.D., B.Sc., B.V.Sc., M.R.C.V.S., Department of Veterinary Clinical Studies, School of Veterinary Medicine, Madingley Road, Cambridge, England.

PAGE

CLINICAL

Prevention, Diagnosis and Treatment of Prolonged Apnoea 384

By H. C. Churchill Davidson, M.D., F.F.A.R.C.S., and R. P. Wise, M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, St. Thomas's Hospital, London, England.

The Use of the Goldman Halothane Vaporizer in the Closed Circuit ... 388

By F. R. Gusterson, B.Sc., M.B., B.S., F.F.A.R.C.S., and J. M. Clark, M.B., B.S., D.A., Worthing Group of Hospitals, Worthing, England.

WAIKATO HOSPITAL BOARD, NEW ZEALAND 363

THE LOVELACE CLINIC, U.S.A. 371

BOOK REVIEWS 383, 393, 394

JOHN SHERRATT & SON *Publishers* **PARK ROAD ALTRINCHAM ENGLAND**